

OPTOELECTRONIC BIOSENSING FOR POINT-OF-CARE DIAGNOSTICS

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**CENTRE FOR SENSORS, INSTRUMENTATION AND
CYBER PHYSICAL SYSTEM ENGINEERING**

INDIAN INSTITUTE OF TECHNOLOGY DELHI

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by

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PHYSICAL SYSTEM ENGINEERING**

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CERTIFICATE

This is to certify that the thesis entitled “**OPTOELECTRONIC BIOSENSING FOR POINT-OF-CARE DIAGNOSTICS**” being submitted by **Ms. RITAMBHARA** to the **INDIAN INSTITUTE OF TECHNOLOGY DELHI** for the award of the degree of “**DOCTOR OF PHILOSOPHY**”, is a record of the authentic research work carried out by him under our supervision and guidance. He has fulfilled all the requirements for submission of this thesis, which to the best of our knowledge has reached the required standard.

The material contained in this thesis has not been submitted in part or full to any other University or Institute for the award of any other degree.

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Date:



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Abstract

Point-of-care (PoC) technologies can immensely contribute to the healthcare system for a large section of the population. These technologies can provide better patient-centric care, and hence can increase the contribution to healthcare administration and overall economic growth. A World Health Organization (WHO) report states that out of all member countries, the ratio of physicians to the human population is 1:1000 in 44% of the countries, and the ratio is even worse for developing countries like India, wherein, for a population of 10,189, there is only one physician. In most countries, medical infrastructure is inadequate to cater to the needs of the vast population. Hence, the need to explore a viable alternative to the central lab facilities is enormous. PoC diagnostic systems, by virtue of being intelligent, accurate and portable; can play an important role in making the healthcare system more patient-centric and affordable.

Based upon the technologies involved, sample handling mechanism and the form factor etc., PoC systems can be categorized in many groups. Paper-based PoC systems, that employ a paper-based platform for sample handling, give an advantage over other PoC systems as they are portable and cost-effective and can truly fulfil ASSURED criteria. However, paper-based devices usually suffer low specificity and sensitivity at lower concentration values of analyte due to minute variation in spectral values with changes in concentration. Also, subjective interpretation of colors, even along with the color chart, differs from individual to individual and requires perfect color vision. Replacing the visual inspections by a reader or sensor to quantify these color changes can overcome these biases and may yield a better diagnosis. The quantification can be performed by capturing the images of the test strips using the camera of a smartphone which act as an analyzer, suitably integrated with the sensing platform. However, different factors of ambient illumination conditions (color temperature of ambient light, angle of incident light with respect to strip, distance of smartphone with respect to strip) and camera settings (Field-of-view(FOV), Exposure) can change the colorimetric measurement. Camera

settings which are automatically adjusted to give an image with the best appearance can significantly vary with the external illumination conditions and with smartphone make and model. Also, even if the illumination conditions are made uniform using the delicate hardware design; camera settings (Focus, exposure, Field of view (FOV)) of the smartphone; effectively change the colorimetric values at the test strip. This thesis presents the smartphone-based PoC system that estimates the concentration of the analytes in the urine sample by quantifying the colorimetric changes in the test strips when the sample under investigation is introduced on to it. In the present work, we have developed robust algorithms enabling the colorimetric measurements independent of the variations in the ambient illumination and camera settings parameters/conditions.

After image acquisition using a smartphone, the camera sensors of the smartphone can exhibit different aspect ratios, which produce different resolution images. On the other hand, smartphone camera settings such as Focus and exposure values can alter colorimetric values. In smartphone cameras, autofocus is achieved using contrast detection as a parameter, which varies with ambient lighting and the background, as it detects the maximum intensity gradient part of the image. Also, the image acquired using a smartphone can exhibit different brightness values that correspond to the exposure of the camera and its shutter speed. The exposure value, which varies from $-EV_{\min}$ (Exposure Value) to $+EV_{\max}$, also varies with smartphone make and model. Hence, even though the external hardware can mitigate ambient light conditions, camera settings can alter colorimetric values and in this thesis, these problems have been addressed. Further, to achieve the ASSURED criteria, a truly portable device for the low resource settings, with minimum hardware requirements is very much desirable. Add-on devices have the limitation of external hardware. Also, as the camera position changes with smartphone models, the design of the add-on device needs to be changed with every smartphone model. In this thesis, the limitation of external hardware has been addressed by

realizing an accessory-free, smartphone-based system for the quantification of the microalbumin for kidney disease diagnosis. The proposed accessory-free system addresses the parameters associated with the ambient illumination conditions (Color temperature, shadow) and the smartphone variation, which was otherwise taken care of by the add-on accessory.

This thesis presents the algorithmic solutions for colorimetric measurement in two smartphone-based settings: 1) add-on device and 2) accessory-free system. In the context of an add-on device attached to smartphone, the effect of camera settings (FOV, Focus, and Exposure) has been investigated for colorimetric measurement. A software framework is demonstrated for the quantification of hormonal lines. After image acquisition using the add-on device, a multi-scale template matching method has been introduced to acquire fixed resolution images, that produce a fixed aspect ratio image for further processing. To achieve a fixed focus point on hormonal lines, an algorithm was designed to achieve fixed focus point. Further, the fixed value of exposure was achieved by designing an algorithm, where n number of images were captured with different exposure values ranging from minimum to zero value of exposure and stored in the database. Further, the strip area was segmented out from the image by localization using the template matching method, followed by segmentation. A correlation value of 0.99 was achieved on 300 patient samples using an add-on device. However to achieve the objective of accessory-free colorimetric measurement, an accessory-free system for quantification of albumin was designed and developed. A study was conducted to observe the effect of ambient illumination (Color temperature, shadow, incident angle on strip) conditions and camera settings (Focus and ISO) in ambient illumination conditions. The effect of the shadow of smartphone on the strip is studied and a method was devised to compensate for its effect. The smartphone camera with “Flash On” mode is used and the classification of nine different concentrations of albumin is performed using machine learning classifiers (Logistic regression, Support vector machine, Random forest). Here, certain color features were observed to be less

invariant with ambient light conditions and smartphone models. An accuracy of 82% was achieved in variable lighting conditions with three different smartphone models. Further, as deep learning models have become more powerful in recent years, in this thesis, a customized CNN model has been developed with few layers along with different color spaces to classify all nine concentration values to get better accuracy. An accuracy of 88% was acquired in different illumination conditions with three different smartphones.

सार

प्वाइंट-ऑफ-केयर (पीओसी) प्रौद्योगिकियां आबादी के एक बड़े हिस्से के लिए स्वास्थ्य सेवा प्रणाली में अत्यधिक योगदान दे सकती हैं। ये प्रौद्योगिकियां बेहतर रोगी-केंद्रित देखभाल प्रदान कर सकती हैं, और इसलिए स्वास्थ्य प्रशासन और समग्र आर्थिक विकास में योगदान बढ़ा सकती हैं। विश्व स्वास्थ्य संगठन (डब्ल्यूएचओ) की एक वर्णन में कहा गया है कि सभी सदस्य देशों में, 44% देशों में चिकित्सकों का मानव आबादी से अनुपात 1:1000 है, और भारत जैसे विकासशील देशों के लिए यह अनुपात और भी खराब है, जिसमें, 10,189 की आबादी में केवल एक चिकित्सक है। अधिकांश देशों में, विशाल आबादी की जरूरतों को पूरा करने के लिए चिकित्सा अवसंरचना अपर्याप्त है। इसलिए, केंद्रीय प्रयोगशाला सुविधाओं के लिए एक व्यवहार्य विकल्प तलाशने की बहुत आवश्यकता है। पीओसी निदान व्यवस्था, बुद्धिमान, सटीक और वाह्य होने के कारण; स्वास्थ्य सेवा प्रणाली को अधिक रोगी केंद्रित और किफायती बनाने में महत्वपूर्ण भूमिका निभा सकता है।

शामिल प्रौद्योगिकियों के आधार पर, नमूना संचालन तंत्र और प्रपत्र कारक आदि, पीओसी प्रणालियों को कई समूहों में वर्गीकृत किया जा सकता है। पेपर-आधारित पीओसी सिस्टम, जो नमूना संभालना के लिए पेपर-आधारित पटल को नियोजित करते हैं, अन्य पीओसी व्यवस्था पर एक फायदा देते हैं क्योंकि वे वाह्य और लागत प्रभावी हैं और वास्तव में सुनिश्चित मानदंडों को पूरा कर सकते हैं। हालांकि, पेपर-आधारित उपकरण आमतौर पर कम विशिष्टता और कम एकाग्रता मूल्यों पर संवेदनशीलता का सामना करते हैं, जो कि एकाग्रता में परिवर्तन के साथ वर्णक्रमीय मूल्यों में मिनट भिन्नता के कारण होता है। साथ ही, रंगों की व्यक्तिपरक व्याख्या, यहां तक कि रंग चार्ट के साथ, हर व्यक्ति में अलग-अलग होती है और इसके लिए सही रंग दृष्टि की आवश्यकता होती है। इन रंग परिवर्तनों को मापने के लिए एक पाठक या संवेदक द्वारा दृश्य निरीक्षण को बदलने से इन पूर्वाग्रहों को दूर किया जा सकता है और बेहतर निदान मिल सकता है। एकचल दूरभाष के छायाचित्रक का उपयोग करके परीक्षण पट्टी की छवियों को प्रग्रहण करके परिमाणीकरण किया जा सकता है जो एक विश्लेषक के रूप में कार्य करता है, जो

संवेदन पटल के साथ उपयुक्त रूप से एकीकृत होता है। हालांकि, परिवेश रोशनी की स्थिति (परिवेश प्रकाश का रंग तापमान, पट्टी के संबंध में घटना प्रकाश का कोण, पट्टी के संबंध में चल दूरभाष की दूरी) और छायाचित्रक जड़ा हुआ (देखने के क्षेत्र (एफओवी), अनावरण) के विभिन्न कारक बदल सकते हैं वर्णमिति माप। छायाचित्रक जड़ा हुआ जो स्वचालित रूप से सबसे अच्छी उपस्थिति के साथ एक छवि देने के लिए समायोजित की जाती है, बाहरी रोशनी की स्थिति और चल दूरभाष मेक और मॉडल के साथ महत्वपूर्ण रूप से भिन्न हो सकती हैं। इसके अलावा, भले ही नाजुक धातु सामग्री रचना का उपयोग करके रोशनी की स्थिति को समान बनाया गया हो; चल दूरभाष की छायाचित्रक जड़ा हुआ (किरणकेन्द्र, अनावरण, देखने के क्षेत्र (एफओवी)); परीक्षण पट्टी पर वर्णमिति मूल्यों को प्रभावी ढंग से बदलें। यह शोध प्रबन्ध चल दूरभाष-आधारित पीओसी प्रणाली प्रस्तुत करती है जो जांच के तहत नमूना पेश किए जाने पर परीक्षण पट्टी में वर्णमिति परिवर्तनों की मात्रा निर्धारित करके मूत्र के नमूने में विश्लेषण की एकाग्रता का अनुमान लगाती है। वर्तमान कार्य में, हमने परिवेशी रोशनी और छायाचित्रक जड़ा हुआ मापदंडों / स्थितियों में भिन्नता से स्वतंत्र वर्णमिति माप को सक्षम करने वाले मजबूत कलन-विधि विकसित किए हैं।

चल दूरभाष का उपयोग करके छवि अधिग्रहण के बाद, चल दूरभाष के छायाचित्रक संवेदक विभिन्न पहलू अनुपात प्रदर्शित कर सकते हैं, जो विभिन्न विभेदन छवियां उत्पन्न करते हैं। दूसरी ओर, चल दूरभाष छायाचित्रक जड़ा हुआ जैसे किरणकेन्द्र और अनावरण मान वर्णमिति मानों को बदल सकते हैं। चल दूरभाष छायाचित्रक में, एक मापदण्ड के रूप में व्यतिरेक खोज का उपयोग करके स्वतः केंद्रबिन्दु हासिल की जाती है, जो अलग-अलग होती है परिवेश प्रकाश और पृष्ठभूमि, क्योंकि यह छवि के अधिकतम तीव्रता ढाल वाले हिस्से का पता लगाता है। साथ ही, चल दूरभाष का उपयोग करके प्राप्त की गई छवि विभिन्न चमक मान प्रदर्शित कर सकती है जो छायाचित्रक के अनावरण और इसकी शटर गति के अनुरूप होती है। अनावरण मूल्य, जो न्यूनतम (अनावरण मूल्य) से अधिकतम तक भिन्न होती है, चल दूरभाष नमूना के साथ भी भिन्न होती है। इसलिए, भले ही बाहरी धातु सामग्री परिवेश प्रकाश की

स्थिति को कम कर सकता है, छायाचित्रक जड़ा हुआ वर्णमिति मूल्यों को बदल सकती हैं और इस शोध प्रबन्ध में इन समस्याओं को संबोधित किया गया है। इसके अलावा, सुनिश्चित मानदंडों को प्राप्त करने के लिए, कम संसाधन जड़ा हुआ के लिए वास्तव में वाह्य प्रणाली, न्यूनतम धातु सामग्री आवश्यकताओं के साथ बहुत वांछनीय है। अतिरिक्त उपकरण में बाहरी धातु सामग्री की सीमा होती है। साथ ही, चूंकि चल दूरभाष मॉडल के साथ छायाचित्रक की स्थिति बदलती है, अतिरिक्त उपकरण के डिज़ाइन को प्रत्येक चल दूरभाष नमूना के साथ बदलने की आवश्यकता होती है। इस शोध प्रबन्ध में, गुर्दे की बीमारी के निदान के लिए माइक्रोएल्ब्यूमिन की मात्रा का ठहराव के लिए एक सहायक-मुक्त, चल दूरभाष - आधारित प्रणाली को साकार करके बाहरी धातु सामग्री की सीमा को संबोधित किया गया है। प्रस्तावित सहायक सिस्टम परिवेशी रोशनी की स्थिति (रंग तापमान, छाया) और चल दूरभाष स्मार्टफोन भिन्नता से जुड़े मापदंडों को संबोधित करता है, जो अन्यथा अतिरिक्त उपकरण सहायक द्वारा ध्यान रखा जाता था।

यह शोध प्रबन्ध दो चल दूरभाष-आधारित जड़ा हुआ में वर्णमिति माप के लिए कलन-विधि समाधान प्रस्तुत करता है: 1) अतिरिक्त उपकरण और 2) सहायक-मुक्त प्रणाली। चल दूरभाष से जुड़े एक अतिरिक्त उपकरण डिवाइस के संदर्भ में, वर्णमिति माप के लिए छायाचित्रक जड़ा हुआ (देखने के क्षेत्र, किरणकेन्द्र और अनावरण) के प्रभाव की जांच की गई है। हार्मोनल रेखा की मात्रा का ठहराव के लिए एक चल दूरभाष क्रमानुदेश ढांचे का प्रदर्शन किया जाता है। अतिरिक्त उपकरण का उपयोग करके छवि अधिग्रहण के बाद, निश्चित विभेदन छवियों को प्राप्त करने के लिए एक बहु-स्तरीय नमूना मिलान विधि शुरू की गई है, जो आगे की प्रक्रिया के लिए एक निश्चित पहलू अनुपात छवि उत्पन्न करती है। हार्मोनल रेखा पर एक निश्चित किरणकेन्द्र बिंदु प्राप्त करने के लिए, निश्चित किरणकेन्द्र बिंदु प्राप्त करने के लिए एक कलन-विधि तैयार किया गया था। इसके अलावा, एक कलन-विधि रचना करके अनावरण का निश्चित मूल्य प्राप्त किया गया था, जहां छवियों की संख्या को विभिन्न अनावरण मानों के साथ प्रग्रहण किया गया था, जो अनावरण के न्यूनतम से शून्य मान तक थे और आँकड़ासंचय में संग्रहीत थे। इसके

अलावा, पट्टी क्षेत्र को नमूना मिलान पद्धति का उपयोग करके स्थानीयकरण द्वारा छवि से अलग किया गया था, इसके बाद विभाजन किया गया था। एक अतिरिक्त उपकरण का उपयोग करके 300 रोगी नमूनों पर 0.99 का सहसंबंध मान प्राप्त किया गया था। हालांकि, गौण-मुक्त वर्णमिति माप के उद्देश्य को प्राप्त करने के लिए, एल्ब्यूमिन की मात्रा का निर्धारण करने के लिए एक सहायक-मुक्त प्रणाली को विकसित किया गया था। परिवेश रोशनी (रंग तापमान, छाया, पट्टी पर घटना कोण) स्थितियों और छायाचित्रक जड़ा हुआ (किरणकेन्द्र और आईएसओ) के परिवेश रोशनी की स्थिति में प्रभाव का निरीक्षण करने के लिए एक अध्ययन किया गया था। चल दूरभाष की परछाई के पट्टी पर पड़ने वाले प्रभाव का अध्ययन किया जाता है और इसके प्रभाव की भरपाई के लिए एक तरीका तैयार किया जाता है। " ज्योति लगातार " प्रणाली वाले चल दूरभाष छायाचित्रक का उपयोग किया जाता है और यंत्र अधिगम वर्गीकारक (लॉजिस्टिक रिग्रेशन, सपोर्ट वेक्टर मशीन, रैंडम फ़ॉरेस्ट) का उपयोग करके एल्ब्यूमिन की नौ अलग-अलग सांद्रता का वर्गीकरण किया जाता है। यहां, परिवेश प्रकाश की स्थिति और चल दूरभाष नमूना के साथ कुछ रंग विशेषताओं को कम अपरिवर्तनीय देखा गया। तीन अलग-अलग चल दूरभाष नमूना मॉडल के साथ परिवर्तनीय प्रकाश व्यवस्था की स्थिति में 82% की सटीकता हासिल की गई थी। इसके अलावा, जैसा कि हाल के वर्षों में गहन शिक्षण मॉडल अधिक शक्तिशाली हो गए हैं, इस शोध प्रबन्ध में, बेहतर सटीकता प्राप्त करने के लिए सभी नौ एकाग्रता मूल्यों को वर्गीकृत करने के लिए अलग-अलग रंग रिक्त स्थान के साथ कुछ परतों के साथ एक अनुकूलित कृत्रिम तंत्रिका नेटवर्क नमूना विकसित किया गया है। तीन अलग-अलग चल दूरभाष के साथ अलग-अलग रोशनी की स्थिति में 88% की सटीकता हासिल की गई थी।

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List of Abbreviations

PoC	Point-of-Care
WHO	World health Organisation
PCR	Polymerase chain reaction
ASSURED	Affordable, Sensitive, Specific, User friendly, Rapid and robust, Equipment-free, Delivered.
LED	Light emitting diode
CMOS	Complementary metal oxide semiconductor
ROI	Region of interest
RGB	Red, Green, Blue
ANN	Artificial neural network
CNN	Convolutional neural network
LR	Logistic regression
SVM	Support vector machine
RF	Random forest
LH	lutinizing hormone
E3G	Estrone-3-gluconoride
FOV	Field-of-view
IOT	Internet of things
DD	Device detection
SD	Strip detection
CT	Color temperature
BP	Brightest point

EV	Exposure value
R_{avg}	Mean value of red channel
ISP	Image sensor pipeline
CCM	Color correction matrix
OD	Optical density
ELISA	Enzyme linked immunoassay
GFR	Glomerular filtration rate
ReLU	Rectified linear unit