

A Tribute to Mahamana

Pt. Madan Mohan Malviya ji

Dedicated

To

My Son

Karanjeet Chowdhury

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I, Md. Koushik Chowdhury, declare that the work embodied in this Ph.D. thesis is my own bonafide work carried out under the supervision of Dr. Neeraj Sharma and Dr. Shiru Sharma for a period of about 4 years and 10 months from March 2011 to December 2015 at the School of Biomedical Engineering, Indian Institute of Technology (Banaras Hindu University), Varanasi. The matter embodied in this thesis has not been submitted for the any other degree/diploma.

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(Md. Koushik Chowdhury)

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List of Abbreviations

ADA	: American Diabetes Association
AHA	: American Heart Association
AM	: Amplitude Modulation
BGL	: Blood Glucose Level
CE	: Conformité Européenne (European Conformity)
CEG	: Clarke Error Grid
CGMS	: Continuous Glucose Monitoring System
CUSUM	: Cumulative Sum
CI	: Confidence Interval
DCCT	: Diabetes Control and Complications Trial
D-Glucose	: Dextro-Glucose
DM	: Diabetes Mellitus
DSO	: Digital Storage Oscilloscope
EGA	: Error Grid Analysis
EDTA	: Ethylene Di-amine Tetra-acetic Acid
FDA	: Food and Drug Administration
FFT	: Fast Fourier Transform
FM	: Frequency Modulation
FPG	: Fasting Plasma Glucose
GHb	: Glycosylated Hemoglobin
GmbH	: Gesellschaft mit beschränkter Haftung
HbA1c	: Glycated Hemoglobin
IC	: Integrated Circuit
IDF	: International Diabetes Federation
IFG	: Impaired Fasting Glucose
IGT	: Impaired Glucose Tolerance
IMS-BHU	: Institute of Medical Sciences-Banaras Hindu University
IR	: Infra Red
ISO	: International Organization for Standardization
Inc.,	: Incorporation
LASER	: Light Amplification Simulation Emission Radiation
LED	: Light Emitting Diode
MAE	: Mean Absolute Error
%MARE	: Percentage of Mean Absolute Relative Error
MdAE	: Median Absolute Error
%MdARE	: Percentage of Median Absolute Relative Error
MATLAB	: Matrix Laboratory
MIR	: Mid Infra Red

NIR: Near Infra RedOCT: Optical Coherence TomographyOGTT: Oral Glucose Tolerance TestPA: Photo AcousticP-BGL: Predicted-Blood Glucose LevelPBS: Phosphate Buffer SolutionPP: Post Prandial
OGTT: Oral Glucose Tolerance TestPA: Photo AcousticP-BGL: Predicted-Blood Glucose LevelPBS: Phosphate Buffer Solution
PA: Photo AcousticP-BGL: Predicted-Blood Glucose LevelPBS: Phosphate Buffer Solution
P-BGL: Predicted-Blood Glucose LevelPBS: Phosphate Buffer Solution
PBS : Phosphate Buffer Solution
I I
PP · Post Prandial
PEG : Parkes Error Grid
PM : Phase Modulation
RAD : Relative Absolute Difference
RBC : Red Blood Corpuscles
R-BGL : Reference-Blood Glucose Level
RIGMD : Reverse Iontophoresis based Glucose Monitoring Device
RMSE : Root Mean Squared Error
r value : Correlation Coefficient
SD : Standard Deviation
SNR : Signal to Noise Ratio
SEP : Standard Error of Prediction
TM : Trade Mark
THb : Total Hemoglobin
UK : United Kingdom
UKPSD : United Kingdom Prospective Diabetes Study
USA : United States of America
USD : United States Dollar
US\$: United States Dollar
USR : Ultra Sound Receiver
UST : Ultra Sound Transmitter
UV : Ultra Violet
WHO: World Health Organization

Preface of the Thesis

Diabetes Mellitus has progressed as an important healthcare endemic of the contemporary world. The diabetic subject needs to monitor their Blood Glucose Level regularly for three to four times per day for circumventing the terminal stage medical complexities and expenses. The invasive device based blood glucose monitoring comprises painful procedures, mental agony, and infection liabilities and high cost per measurement. For all these reasons, at present a new noninvasive technique for blood glucose measurement is extremely demanding. In perspective of addressing the requirement for this necessity, the present thesis work objective is to validate our indigenously developed noninvasive technique for blood glucose measurement in the human subjects. The present thesis contains seven subsequent chapters as follows: Introduction; Literature Review; Concept, prototype fabrication, and methodology; Effect of glucose concentration on light transmission; Clinical investigation based results; Discussion; Conclusion and future recommendations.

Chapter-1 Introduction: This chapter briefly introduces the present scenario regarding regular blood glucose monitoring in diabetic subjects and the essential need for noninvasive blood glucose monitoring technique. This chapter briefly portrays the aims and objectives, research contributions and outcome of the present thesis work. The thesis organization section concisely highlights all the chapters present in this thesis. Further, it contains the full list of published research articles and honors received.

Chapter-2 Literature Review: This chapter provides brief illustration about Diabetes Mellitus, its related medical complications, and blood glucose monitoring techniques. This section concisely describes various developing noninvasive blood glucose measuring methods and their respective prototypes, mechanism for physiological blood glucose regulation and skin tissue characteristics, optical clearing effect related studies, invivo and in-vitro experiments, Glycated hemoglobin and blood pressure relation with blood glucose, and various additional effects.

Chapter-3 Concept, prototype fabrication, and methodology: This chapter represents the combined concept of Amplitude Modulated Ultrasonic waves and Infrared light-based approach for noninvasive measurement of blood glucose levels. This chapter describes the block diagram of our fabricated prototype unit including its light wavelength

and ultrasound frequency selection criterions, calibration aspects, in-vitro, and preliminary in-vivo results. Further, this chapter includes concise description of the Clarke error grid and statistical analysis based approaches for measuring the accuracy performance of our prototype unit in measuring predicted blood glucose levels.

Chapter-4 Effect of glucose concentration on light transmission: This chapter represents the clinical study based on the optical clearing effect of blood glucose concentration over light transmission.

Chapter-5 Clinical investigation based results: This chapter reports the clinical investigation based results of our noninvasive technique applied over (i) healthy nondiabetic, (ii) pre-diabetic, and (iii) diabetic human subjects for blood glucose measurement purposes. All the clinical investigations mainly focus over noninvasive blood glucose level determining aspects and its clinically significant correlations with the invasive blood glucose measurements. Various clinical studies reported here include (i) Standard Oral Glucose Tolerance tests, (ii) Blood glucose level measurements during fasting stage, postprandial stage and random stage respectively. Further, it contain results about the clinical correlations of the blood glucose levels relationship with the (i) Glycated hemoglobin (HbA1c) concentration and (ii) blood pressure values in healthy normal and diabetic subjects. This section also includes comparison of our results with the published results to measure the performance index of our prototype unit in noninvasive blood glucose measurement.

Chapter-6 Discussion: This chapter contains brief description of our overall study and the medical importance of our results. Henceforth, it compares our overall blood glucose measurements with the published data available in the English language based research literatures. Further, various statistical methods evaluates the statistical significance of our overall results.

Chapter-7 Conclusion and recommendations for future work: This chapter presents the conclusion of the present thesis work and direction for future research work. Afterwards, the reference portion enlists overall research papers utilized to pursue this present work.