

CONTENTS

	Page No.
List of Tables	ix
List of Figures	xii
List of Abbreviations	xvii
Preface of the Thesis	xix

1. INTRODUCTION	1-10
------------------------	-------------

1.1	Background	1
1.2	Problem statement and Research motivation	1
1.3	Aim and Objective of the present thesis work	6
1.4	Research Contributions of the present thesis work	7
1.5	Outcome of the present thesis work	7
1.6	Thesis Organization	8

2. LITERATURE REVIEW	11-51
-----------------------------	--------------

2.1	Overview	12
2.2	Classification of Diabetes Mellitus (DM)	12
2.2.1	Pre-diabetics with Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG) Conditions	12
2.3	Complications associated with Diabetes Mellitus (DM)	13
2.4	Monitoring Blood Glucose Levels	13
2.4.1	Invasive technique based approach	13
2.4.1.2	User-Friendly Invasive Blood Glucose Meters	14
2.4.2	Semi-invasive technique based approach	16
2.4.3	Non-invasive technique based approaches	17
2.5	Noninvasive optical and other technologies for blood glucose level measurements	17
2.5.1	Fluorescent Spectroscopy	17
2.5.1.1	Significance	18
2.5.1.2	Limitations	18
2.5.2	Photo Acoustic (PA) Spectroscopy	19
2.5.2.1	Significance	20
2.5.2.2	Limitations	20
2.5.3	Optical Coherence Tomography (OCT)	20
2.5.3.1	Significance	21

2.5.3.2	Limitations	21
2.5.4	Polarization Spectroscopy	21
2.5.4.1	Significance	22
2.5.4.2	Limitations	23
2.5.5	Ocular Spectroscopy	23
2.5.5.1	Significance	23
2.5.5.2	Limitations	23
2.5.6	Raman Spectroscopy	23
2.5.6.1	Significance	24
2.5.6.2	Limitations	24
2.5.7	Occlusion Spectroscopy	25
2.5.7.1	Significance	25
2.5.7.2	Limitations	25
2.5.8	Bio-impedance Spectroscopy	25
2.5.8.1	Significance	26
2.5.8.2	Limitations	26
2.5.9	Electromagnetic Sensing	26
2.5.9.1	Significance	27
2.5.9.2	Limitations	27
2.5.10	Reverse Iontophoresis	27
2.5.10.1	Significance	27
2.5.10.1	Limitations	27
2.5.11	Mid-Infrared (MIR) Spectroscopy	28
2.5.11.1	Significance	29
2.5.11.2	Limitations	29
2.5.12	Near Infrared (NIR) Spectroscopy	29
2.5.12.1	Significance	30
2.5.12.2	Limitations	31
2.5.13	Thermal Spectroscopy	31
2.5.13.1	Significance	31
2.5.13.2	Limitations	31
2.5.14	Ultrasound Modulated Optical Technique	31
2.5.14.1	Significance	32
2.5.14.2	Limitations	32
2.6	Various developing Noninvasive Glucometers and their respective Approval status	36
2.6.1	Gluco-Track™ by Integrity Applications Ltd., Ashkelon, Israel	36
2.6.2	Portable Blood Glucose meter by Glove Instruments, USA	36
2.6.3	Noninvasive Glucometer based on Microwave Technology by Baylor University, Texas, USA	36

2.6.4	Noninvasive Glucometer based on Near Infrared Optical Spectroscopy and Multivariate Tools by InLight Solutions, Albuquerque, New Mexico, USA	36
2.6.5	Noninvasive Glucometer by LighTouch Medical Inc., Pennsylvania, USA	37
2.6.6	I-Sugar-X Noninvasive Glucometer by Freedom Meditech Inc., California, USA	37
2.6.7	Contact Lens based Continuous Glucose Monitoring by University of Washington, USA	37
2.6.8	Symphony tCGM by Echo Therapeutics Inc., Philadelphia, USA	37
2.6.9	Multisensory Glucose Monitoring System by Biovotion AG, Zürich, Switzerland	38
2.6.10	TensorTip CoG-Combo Glucometer by Cnoga Medical Ltd., Akiva, Israel	38
2.6.11	Noninvasive Glucometer by C8 Medisensors by California-based Company, USA	38
2.6.12	Easy Check Positive ID (Identification) Noninvasive Glucometer by Positive ID Corporation, the Israel-based Company	38
2.6.13	Eye sense Noninvasive Glucometer by EyeSense GmbH, Großostheim, Germany	39
2.6.14	Glucoband Noninvasive Glucometer by Calisto Medical Inc., Texas, USA	39
2.6.15	Occlusion Spectroscopy based Noninvasive Glucometer by OrSense Ltd., Petah-Tikva, Israel	39
2.6.16	Noninvasive Glucose monitoring device by Biosensor Inc., Newyork, USA	39
2.6.17	ClearPath DS-120 by Freedom Meditech, Inc., California, USA	40
2.6.18	TANGTEST Blood Glucose Meter based on Optical Technology, USA	40
2.6.19	Reverse Iontophoresis based Glucose Monitoring Device (RIGMD), Seoul, Korea	40
2.6.20	Aprise by Glucon Inc., Colorado, USA	41
2.6.21	Sentris-100 by GlucoLight Corporation, Pennsylvania, USA	41
2.7	Noninvasive Glucometer Devices that received Regulatory Approvals	41
2.7.1	Diasensor, BICO Inc., Pittsburgh, USA	41
2.7.2	Pendra by Pendragon Medical Ltd., Zurich, Switzerland	42
2.7.3	Glucowatch by Cygnus Inc., California, USA	42
2.7.4	SCOUT DS system by Vera Light Inc., Manitoba, Canada	43
2.8	Blood glucose	43
2.8.1	Nutritional carbohydrates	43

2.8.2	Physiological regulation of blood glucose levels	44
2.8.3	Glucose	44
2.9	Human skin tissue	45
2.10	Human fingertip	46
2.11	Optical clearing effect related studies	46
2.12	In-vitro experiments	46
2.13	In-vivo experiments	47
2.13.1	OGTT (Oral Glucose Tolerance Test)	47
2.13.2	HbA1c (Glycated Hemoglobin) levels impact over the blood glucose levels	47
2.13.3	Blood glucose level and blood pressure related studies	48
2.14	Additional effects	49
2.14.1	Machine and Time drift effects	49
2.14.2	Temperature effect	49
2.14.3	Contact interface	50
2.14.4	Location of the body	50
2.15	Conclusion	51

3. CONCEPT, PROTOTYPE FABRICATION, AND METHODOLOGY **52-98**

3.1	Concept for noninvasive blood glucose measurement	53
3.1.1	Absorption spectral analysis	54
3.2	Prototype fabrication	55
3.2.1	Ultrasound frequency selection	55
3.2.2	Light wavelength selection	56
3.3	In-vitro analysis	61
3.3.1	Glucose molecule specificity analysis	61
3.3.2	Glucose molecule sensitivity analysis at 940 nm	62
3.4	Amplitude Modulation (AM) concept and its application in our work	63
3.5	Fabricated prototype descriptions	67
3.5.1	Modulating signal	68
3.5.2	Carrier wave	70
3.5.3	Modulator unit	72
3.5.3.1	Functional descriptions	72
3.5.4	Ultra Sound Transmitter (UST) and Ultra Sound Receiver (USR) units	75
3.5.5	Finger holder unit (Finger probe)	77
3.5.6	Synchronous square wave generator	78
3.5.7	Infrared light source	79
3.5.7.1	940 nm LED wavelength verification	79
3.5.8	Infrared (IR) detector (Photodiode)	80

3.5.9	Signal processing unit	81
3.5.10	Result display	81
3.6	In-vitro experiment	81
3.6.1	In-vitro experiment using glucose in distill water	81
3.6.1.1	Result analysis	82
3.6.2	In-vitro experiment using quasi-finger system	82
3.6.2.1	Study subjects	82
3.6.2.2	Sample preparation	83
3.6.2.3	Result analysis	84
3.7	Preliminary in-vivo analysis	84
3.7.1	Extended in-vivo clinical study	86
3.7.2	Study subjects	86
3.7.3	Experimental phases	87
3.7.3.1	Phase I (a): Before meal intake session in absence of amplitude modulated ultrasound in our prototype	87
3.7.3.2	Phase I (b): Before meal intake Session in presence of amplitude modulated ultrasound in our prototype	88
3.7.3.3	Phase II: One hour after meal intake session in presence of amplitude modulated ultrasound in our prototype	89
3.7.4	Result analysis	91
3.8	Calibration	91
3.9	Inference	92
3.10	Tests methodology	92
3.11	Clarke Error Grid analysis	95
3.12	Statistical analysis	97

4. EFFECT OF GLUCOSE CONCENTRATION ON LIGHT TRANSMISSION **99-109**

4.1	Introduction	100
4.2	Study subjects	101
4.3	Experimental protocol	101
4.4	Peak to peak amplitude measurements for Absolute and Square value calculations	103
4.4.1	Absolute value calculations	103
4.4.2	Square value calculations	105
4.4.3	Result and Discussion	106
4.5	Conclusion	109

5.1	Oral Glucose Tolerance Test based clinical study over healthy non-diabetic subjects	111
5.1.1	Introduction	111
5.1.2	Study subjects	111
5.1.3	Experimental protocol	111
5.1.4	Blood glucose measurement	112
5.1.5	Result and Discussion	112
5.1.6	Conclusion	118
5.2	The effect of different glucose concentrations over blood glucose levels	118
5.2.1	Introduction	118
5.2.2	Study subjects	118
5.2.3	Experimental protocol	119
5.2.4	Blood glucose measurement	119
5.2.5	Result and Discussion	120
5.2.6	Conclusion	124
5.3	Study over pre-diabetic subjects	124
5.3.1	Introduction	124
5.3.2	Glucose sensing in pre-diabetics	125
5.3.3	Study subjects	125
5.3.4	Experimental protocol	125
5.3.5	Blood glucose measurement	126
5.3.6	Result and Discussion	126
5.3.7	Conclusion	130
5.4	Clinical study over Diabetic subjects	130
5.4.1	Introduction	130
5.4.2	Blood glucose supervision	131
5.4.3	Study subjects	131
5.4.4	Experimental protocol	131
5.4.5	Blood glucose measurement	132
5.4.6	Result and Discussion	132
5.4.7	Conclusion	137
5.5	Five daily sessions of blood glucose measurement in a healthy normal and a diabetic subject	137
5.5.1	Introduction	137
5.5.2	Study subjects	138
5.5.3	Experimental protocol	138
5.5.4	Blood glucose measurement	138

5.5.5	Result and Discussion	138
5.5.6	Conclusion	142
5.6	Blood Glucose and Glycated Hemoglobin relationship	142
5.6.1	Introduction	142
5.6.2	Study subjects	143
5.6.3	Experimental protocol	143
5.6.4	Invasive and Noninvasive determination of fasting blood glucose levels	144
5.6.5	Glycated Hemoglobin (HbA1c) levels measurement	144
5.6.6	Result and Discussion	145
5.6.7	Conclusion	151
5.7	Blood glucose and blood pressure relationship	151
5.7.1	Introduction	151
5.7.2	Study subjects	151
5.7.3	Experimental protocol	151
5.7.4	Blood pressure and blood glucose measurement	152
5.7.4.1	Blood pressure measurement	152
5.7.4.2	Blood glucose measurement	153
5.7.5	Result and Discussion	153
5.7.5.1	Stage I	153
5.7.5.2	Stage II	155
5.7.5.3	Stage III	157
5.7.6	Conclusion	164
5.8	Extended clinical study using OGTT and Random Blood Glucose Level Tests	164
5.8.1	Introduction	164
5.8.2	Study subjects	165
5.8.3	Experimental Procedures	165
5.8.4	Result and Discussion	166
5.8.4.1	Oral glucose tolerance test based result analysis	166
5.8.4.2	Random blood glucose test based analysis	171
5.8.5	Conclusion	175

6. DISCUSSION	176-205
----------------------	----------------

6.1	Introduction	177
6.2	Overall result comparison and evaluation	178
6.2.1	Clarke Error Grid Analysis	178
6.2.2	Parkes Error Grid Analysis	181
6.2.3	Accuracy Measure based analysis	183

6.2.4	Pearson correlation coefficient analysis	190
6.2.5	Rank correlation coefficients analysis	193
6.2.6	Bland-Altman Plot	195
6.2.7	Mountain plot	197
6.2.8	Linear model validity	199
6.2.9	Independent sample t-tests	200
6.2.10	Deming Regression	202
6.2.11	ISO compliance	203
6.3	Conclusion	205

7. CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE WORK 207-211

7.1	Conclusions	208
7.2	Recommendations for future work	210

REFERENCES	212-229
APPENDICES (AI,AII,AIII)	230-234
LIST OF PAPERS, PATENT, AND AWARD PUBLICATIONS	235-237
PERSONAL PROFILE	