1 Glucose: Physiological Norm and Pathology

Lidia I. Malinova and Tatyana P. Denisova

1.1 Introduction .................................................. 2
  1.1.1 Goal ..................................................... 2
  1.1.2 Terms and definitions .................................. 2

1.2 System of Blood Glucose Level Regulation and Carbohydrate Metabolism ............................................. 4
  1.2.1 Glucose transporters ..................................... 4
  1.2.2 Pathways of glucose concentration change: glucose distribution and concentrations in human organism .......... 5
  1.2.3 Regulation of glucose metabolism: main pathways and processes .................................................. 8
  1.2.4 Insulin: the key hormone of glucose metabolism .......... 10
  1.2.5 Endothelium and glucose metabolism ...................... 13

1.3 Glucose and Carbohydrate Metabolism Violations ................................................................. 14
  1.3.1 Diabetes mellitus: glucose — victim or culprit? ......... 14
  1.3.2 Atherosclerosis and coronary artery disease: glucose’s place in pathogenesis .................................. 18

1.4 Blood Glucose Level Monitoring in Clinical Practice ................................................................. 21
  1.4.1 Glucose level regulation system tests: clinical and experimental use .............................................. 21
  1.4.2 Clinical value of blood glucose level measurements ...... 22
  1.4.3 Current state of the problem: unsolved questions .......... 22

1.5 Conclusion ..................................................... 24

1.6 Glossary ....................................................... 25

2 Commercial Biosensors for Diabetes

Vasiliki Fragkou and Anthony P.F. Turner

2.1 Introduction .................................................. 42

2.2 Diabetes Mellitus ............................................. 43
  2.2.1 Type I diabetes ............................................ 43
  2.2.2 Type II diabetes .......................................... 43
  2.2.3 Gestational diabetes ....................................... 43
  2.2.4 Incidence - A major world problem ....................... 44
Table of Contents

3.7 Modeling of Glucose Sensing with Frequency Domain Technique . 86
  3.7.1 Principles of frequency domain technique ....................... 86
  3.7.2 Simulation of frequency domain signals ......................... 88
  3.7.3 Analysis of glucose sensing potentialities of the frequency
domain technique ...................................................... 89
3.8 Conclusion ................................................................. 90

4 Statistical Analysis for Glucose Prediction in Blood Samples by Infrared
Spectroscopy ............................................................... 97
  Gilwon Yoon
  4.1 Introduction ............................................................ 98
  4.2 Selection of Optimal Wavelength Region Based on the First Loading
    Vector Analysis ....................................................... 100
    4.2.1 Optimal wavelength region in the mid infrared ............... 100
    4.2.2 Optimal wavelength region in the near infrared ............ 102
  4.3 Minimization of Hemoglobin Interference .......................... 105
    4.3.1 Hemoglobin influence in the mid infrared region ........... 106
    4.3.2 Hemoglobin influence in the near infrared region .......... 106
  4.4 Independent Component Analysis without Calibration Process ... 108
  4.5 Conclusion .............................................................. 111

5 Near-Infrared Reflection Spectroscopy for Noninvasive Monitoring of
Glucose — Established and Novel Strategies for Multivariate Calibra-
tion ................................................................. 115
  H. Michael Heise, Peter Lampen and Ralf Marbach
  5.1 Introduction ............................................................ 116
  5.2 Experimental Design and Methods .................................... 118
    5.2.1 Patients and calibration design ................................ 118
    5.2.2 Reference measurements and calibration method ............. 119
    5.2.3 Experiments and spectroscopic data ........................... 120
  5.3 Results Obtained by Conventional Calibration and Discussion ... 124
  5.4 Advantages of the “Science-Based” Calibration Method .......... 132
  5.5 Theory and Background ................................................ 133
  5.6 Specificity of Response ................................................. 136
  5.7 Illustration of the Science-Based Calibration Method ............ 141
    5.7.1 Outlook for the novel calibration method ..................... 150
  5.8 Conclusions ............................................................. 151

6 Characterizing the Influence of Acute Hyperglycaemia on Cerebral Hemo-
dynamics by Optical Imaging .............................................. 157
  Qingming Luo, Zhen Wang, Weihua Luo and Pengcheng Li
  6.1 Introduction ............................................................ 157
  6.2 Optical Imaging Techniques of Functional Brain .................. 159
    6.2.1 Laser speckle imaging ........................................... 159
6.2.2 Intrinsic optical signal imaging ........................................ 162
6.3 Influence of Acute Hyperglycaemia on CBF and SD in Rat Cortex . 164
  6.3.1 Long-term monitoring the influence of glucose upon CBF in rat cortex .............................................................. 164
  6.3.2 Optical imaging of hemodynamic response during cortical spreading depression in the normal or acute hyperglycemic rat cortex .............................................................. 167
6.4 Conclusion ................................................................. 169

7 Near-Infrared Thermo-Optical Response of the Localized Reflectance of Diabetic and Non-Diabetic Human Skin 181

  Omar S. Khalil
  7.1 Introduction .............................................................. 182
  7.2 Experimental Setup .................................................... 184
  7.3 Temperature Dependence of $\mu_a$ and $\mu'_s$ of Individual’s Skin .............................................................. 185
  7.4 Temperature Modulation of $\mu_a$ and $\mu'_s$ of Skin Over Prolonged Interaction Between the Optical Probe and Skin ......................... 190
  7.5 Dependence of Thermo-Optical Response of Localized Reflectance of Human Skin on Diabetic State .............................................................. 192
  7.6 Test for Diabetic State .................................................. 193
  7.7 Biological Noise and Glucose Determinations ....................... 194
  7.8 Conclusions .............................................................. 197

8 In Vivo Nondestructive Measurement of Blood Glucose by Near-Infrared Diffuse-Reflectance Spectroscopy 205

  Yukihiro Ozaki, Hideyuki Shinzawa, Katsuhiko Maruo, Yi Ping Du and Sumaporn Kasemsumran
  8.1 Introduction .............................................................. 206
  8.2 Importance of NIR In Vivo Monitoring of Blood Glucose ............ 207
  8.3 The NIR System for Noninvasive Blood Glucose Assay ............... 208
  8.3.1 Outline of the NIR instrument ...................................... 209
  8.3.2 Spectral measurements .............................................. 210
  8.4 NIR Spectra of Human Skin and Built of Calibration Models ........ 210
  8.4.1 NIR spectra of human skin .......................................... 210
  8.4.2 Calibration models .................................................. 211
  8.4.3 Blood glucose assay ................................................. 211
  8.4.4 The regression coefficient characteristics ....................... 214
  8.4.5 The prediction of blood glucose content .......................... 214
  8.5 New Chemometrics Algorithms for Wavelength Interval Selection and Sample Selection and Their Applications to In Vivo Near-Infrared Spectroscopic Determination of Blood Glucose ....................... 217
  8.5.1 Moving window partial least squares regression (MWPLSR) ........ 219
  8.5.2 Changeable size moving window partial least squares (CSMW-PLS) and searching combination moving window partial least squares (SCMWPLS) ................................. 221
8.5.3 Application of MWPLSR and SCMWPLS to noninvasive blood glucose assay with NIR spectroscopy

8.6 Multi-Objective Genetic Algorithm-Based Sample Selection for Partial Least Squares Model Building

8.6.1 Multi-objective genetic algorithm

8.6.2 Sample selection by multi-objective GA in PLS

8.6.3 Applications of multi-objective GA to NIR spectra of human skin

8.7 Region Orthogonal Signal Correction (ROSC) and Its Application to In Vivo NIR Spectra of Human Skin

9 Glucose Correlation with Light Scattering Patterns

Ilya Fine

9.1 Introduction

9.1.1 Clinical need for blood glucose measurement

9.1.2 Current art of noninvasive blood measurements

9.1.3 Red blood cells aggregation phenomena

9.1.4 Shear forces and blood viscosity

9.1.5 Clinical relevance of RBC aggregation

9.1.6 Measurement of RBC aggregation

9.2 Principles of Occlusion Spectroscopy

9.2.1 Aggregation assisted optical signal in vivo

9.2.2 The occlusion spectroscopy system

9.3 Spectro-Kinetic Features of Aggregation Assisted Signal

9.3.1 The parametric slope

9.3.2 Structure of parametric slope in vivo

9.3.3 In vitro measurement of POS signal

9.4 Refractive Index of RBC as a Function of Blood Glucose

9.4.1 Mismatch of refractive index

9.4.2 Mismatch of refractive index as a function of glucose

9.5 Parametric Slope as a Function of BG

9.5.1 Time dependent optical parameters

9.5.2 General expression for the PS

9.6 PS Glucose Dependence for Single RBCs and Small Aggregates

9.6.1 RBC scattering pattern

9.6.2 PS for Mie scattering approximation

9.6.3 PSV as a function of glucose

9.6.4 PSS as function of blood plasma glucose for small aggregates

9.7 PSS in the Framework of WKB Model

9.7.1 WKB approximation

9.7.2 Expression for the K-function

9.7.3 Critical wavelength

9.7.4 Effect of glucose on the light transmission for very long aggregates
9.8 Conclusions ........................................... 273

10 Challenges and Countermeasures in NIR Noninvasive Blood Glucose Monitoring 281
Kexin Xu and Ruikang K. Wang

10.1.1 The principle of blood glucose measurement using near infrared spectroscopy .................................. 282
10.1.2 Noninvasive glucose measurement by diffuse reflectance spectroscopy ............................................. 283
10.1.3 The main questions of noninvasive glucose measurement by NIR spectroscopy .................................. 286

10.2 Factors of Influencing the Measuring Precision of Glucose Monitor 287
10.2.1 The relationship between measuring precision and instrument precision ............................................. 288
10.2.2 An effective calibration method to improve the measuring precision of glucose concentration .......... 289
10.2.3 The influence of sample complexity on measuring precision .............................................................. 290
10.2.4 The optimal pathlength method to improve the measuring precision of glucose concentration .......... 293
10.2.5 Precision analysis of the glucose concentration measurement by diffuse reflectance spectroscopy from dermis layer ............................................................. 295

10.3 Noninvasive Glucose Measurement and Human-Spectrometer Interface Technique 297
10.3.1 The influence of measurement site and position .......... 297
10.3.2 The influence of contact pressure ............................................. 299
10.3.3 The measuring conditions reproducible system (MCRS) and human glucose sensing experiments .......... 304

10.4 Challenges and Solutions in In Vivo Noninvasive Blood Glucose Monitoring 307
10.4.1 The influence of the time dependent variations from physiological background on the glucose measurement ............................................. 307
10.4.2 The floating-reference method solution ............................................. 309
10.4.3 The preliminary experimental validation of the floating-reference method ............................................. 312
10.4.4 Summary ............................................. 315

11 Fluorescence-Based Glucose Biosensors 319
Gerard L. Cotè, M. McShane and M.V. Pishko

11.1 Introduction ............................................. 319
11.2 Historical Review of Fluorescence-Based Glucose Assays ............................................. 321
11.3 Issues Involved with In Vivo Glucose Monitoring Using Fluorescent Sensors ............................................. 321
11.4 Fluorescence-Based Glucose-Binding Protein Assays 324
11.4.1 Concanavalin A-based approaches 325
11.4.2 Engineered glucose-binding proteins 331
11.5 Fluorescence Resonance Energy Transfer Systems for Glucose Monitoring 332
11.5.1 Single-molecule RET systems using dual-labeled engineered proteins 335
11.6 Enzyme-Based Glucose Sensors 336
11.6.1 Apo-glucose oxidase 337
11.7 Boronic Acid Derivatives 338
11.8 Summary and Concluding Remarks 341

12 Quantitative Biological Raman Spectroscopy 353
Wei-Chuan Shih, Kate L. Bechtel and Michael S. Feld
12.1 Introduction 354
12.1.1 Introduction to Raman spectroscopy 354
12.2 Review 356
12.2.1 Semi-quantitative implementation 357
12.2.2 Univariate implementation 357
12.2.3 Multivariate implementation 357
12.3 Quantitative Considerations for Raman Spectroscopy 358
12.3.1 Considerations for multivariate calibration models 359
12.3.2 Fundamental and practical limits 359
12.3.3 Chance or spurious correlation 359
12.3.4 Spectral evidence of the analyte of interest 360
12.3.5 Minimum detection limit 361
12.4 Biological Considerations for Raman Spectroscopy 361
12.4.1 Using near infrared radiation 361
12.4.2 Background signal in biological Raman spectra 362
12.4.3 Heterogeneities in human skin 364
12.5 Instrumentation 364
12.5.1 Excitation light source 365
12.5.2 Light delivery, collection, and transport 365
12.5.3 Spectrograph and detector 366
12.6 Data Pre-Processing 367
12.6.1 Image curvature correction 367
12.6.2 Spectral range selection 369
12.6.3 Cosmic ray removal 370
12.6.4 Background subtraction 370
12.6.5 Random noise rejection and suppression 370
12.6.6 White light correction and wavelength calibration 371
12.6.7 Wavelength selection 371
12.7 In Vitro and In Vivo Studies 371
12.7.1 Model validation protocol and summary statistics 371
12.7.2 Blood serum .................................................. 372
12.7.3 Whole blood .................................................. 373
12.7.4 Human study .................................................. 373
12.8 Toward Prospective Application .............................. 374
  12.8.1 Analyte-specific information extraction using hybrid calibration methods ........................................... 374
  12.8.2 Hybrid linear analysis (HLA) ............................ 375
  12.8.3 Constrained regularization (CR) ........................ 375
  12.8.4 Sampling volume correction using intrinsic Raman spectroscopy .................................................. 377
  12.8.5 Corrections based on photon migration theory ...... 377
  12.8.6 Intrinsic Raman spectroscopy (IRS) .................... 378
  12.8.7 Other considerations and future directions .......... 379
12.9 Conclusion ..................................................... 380

13 Tear Fluid Photonic Crystal Contact Lens Noninvasive Glucose Sensors 387
Sanford A. Asher and Justin T. Baca
  13.1 Importance of Glucose Monitoring in Diabetes Management ................................................................. 388
  13.2 Eye Tear Film .................................................. 389
  13.3 Glucose in Tear Fluid ....................................... 390
    13.3.1 Tear fluid glucose transport .......................... 390
    13.3.2 Tear glucose in diabetic subjects .................... 391
  13.4 Previously Reported Tear Fluid Glucose Concentrations ................................................................. 392
    13.4.1 Previous measurements of tears in extracted tear fluid ............................................................ 392
    13.4.2 Mechanical tear fluid stimulation ..................... 393
    13.4.3 Chemical and non-contact tear fluid stimulation ................................................................. 394
    13.4.4 Non-stimulated tear fluid .............................. 395
  13.5 Recent Tear Fluid Glucose Determinations ................ 396
  13.6 In Situ Tear Glucose Measurements ........................ 400
  13.7 Photonic Crystal Glucose Sensors .......................... 401
  13.8 Summary ..................................................... 409

14 Pulsed Photoacoustic Techniques and Glucose Determination in Human Blood and Tissue 419
Risto Myllylä, Zuomin Zhao and Matti Kinnunen
  14.1 Introduction ................................................ 419
  14.2 Theoretical Aspects of PA Techniques Used in Glucose Measurements .................................................. 422
    14.2.1 Cylindrical PA source in a weakly absorbing liquid ................................................................. 423
    14.2.2 Plane PA source in strongly absorbing and scattering tissues .................................................. 425
    14.2.3 Spherical PA source ...................................... 428
  14.3 Optical Sources and Detectors ............................. 430
    14.3.1 Optical sources ......................................... 430
    14.3.2 PA detectors ............................................. 432
14.4 PA Glucose Determination .................................................. 437
  14.4.1 In vitro glucose studies .............................................. 438
  14.4.2 In vivo noninvasive glucose determination ...................... 443
14.5 Problems and Future Perspectives ...................................... 445

15 A Noninvasive Glucose Sensor Based on Polarimetric Measurements Through the Aqueous Humor of the Eye 457
Gerard L. Côté and Brent D. Cameron
15.1 Introduction ................................................................. 458
15.2 Theory of Polarized Light for Detecting Chemical Compounds .... 458
15.3 The Anterior Chamber of the Eye as a Site for Polarimetric Glucose Monitoring .................................................. 462
  15.3.1 Why use the eye? ...................................................... 462
  15.3.2 The anatomy and physiology of the eye toward glucose mon­
        itoring ................................................................. 463
  15.3.3 Corneal curvature and birefringence .............................. 465
15.4 Polarimetric Glucose Monitoring Using a Single Wavelength .... 469
15.5 Measurement of Optical Rotatory Dispersion of Aqueous Humor
        Analytes ........................................................................ 470
15.6 Corneal Birefringence Simulation and Experimental Measurement 475
15.7 Dual Wavelength (Multi-Spectral) Polarimetric Glucose Moni­
        toring ......................................................................... 480
15.8 Concluding Remarks Regarding the Use of Polarization for Glucose
        Monitoring ....................................................................... 481

16 Noninvasive Measurements of Glucose in the Human Body Using Polarimetry and Brewster-Reflection Off of the Eye Lens 487
Luigi Rovati and Rafat R. Ansari
16.1 Introduction ................................................................. 488
16.2 Basic Theory ................................................................. 489
16.3 Anatomy and Properties of the Human Eye of Interest for Polarimet­
        ric Measurements ......................................................... 490
  16.3.1 Polarization effects in the eye’s anterior chamber ............. 490
  16.3.2 The Navarro eye model ............................................... 491
16.4 Optical Access to the Aqueous: Tangential Path and Brewster Scheme
        Approaches ................................................................. 493
  16.4.1 Tangential path approach ............................................. 493
  16.4.2 Brewster scheme ....................................................... 493
16.5 Glucose Sensor Based on the Brewster Scheme .................... 498
  16.5.1 Working principle ...................................................... 498
  16.5.2 Angle detection unit .................................................. 499
  16.5.3 Experimental set-up ................................................... 500
16.6 Performance of the Glucose Sensor Based on the Brewster Scheme 501
  16.6.1 Theoretical analysis .................................................. 502
16.6.2 In vitro experiments .................................................. 516
16.7 Conclusion .................................................................. 523

17 Toward Noninvasive Glucose Sensing Using Polarization Analysis of Multiply Scattered Light 527
Michael F. G. Wood, Nirmalya Ghosh, Xinxin Guo and I. Alex Vitkin
17.1 Introduction ................................................................. 528
17.2 Polarimetry in Turbid Media: Experimental Platform for Sensitive Polarization Measurements in the Presence of Large Depolarized Noise .................................................. 530
17.3 Polarimetry in Turbid Media: Accurate Forward Modeling Using the Monte Carlo Approach ................................................................................................................. 536
17.4 Tackling the Inverse Problem: Polar Decomposition of the Lumped Mueller Matrix to Extract Individual Polarization Contributions .................................................................. 540
17.5 Monte Carlo Modeling Results for Measurement Geometry, Optical Pathlength, Detection Depth, and Sampling Volume Quantification ..................................................... 547
17.6 Combining Intensity and Polarization Information via Spectroscopic Turbid Polarimetry with Chemometric Analysis .......................................................... 553
17.7 Concluding Remarks on the Prospect of Glucose Detection in Optically Thick Scattering Tissues with Polarized Light .......................................................... 558

18 Noninvasive Monitoring of Glucose Concentration with Optical Coherence Tomography 563
Rinat O. Esenaliev and Donald S. Prough
18.1 Introduction ................................................................. 564
18.2 Noninvasive Optical Techniques for Glucose Monitoring .......................................................... 566
18.3 Optical Coherence Tomography ........................................ 567
18.4 Experimental Setup ...................................................... 569
18.5 Studies in Tissue Phantoms ............................................. 570
18.6 Animal Studies ............................................................ 571
18.7 Specificity Studies ........................................................ 572
18.8 Clinical Studies ............................................................ 574
18.9 Mechanisms of Glucose-Induced Changes in Optical Properties of Tissue ..................................................... 576
18.10 Conclusions ............................................................... 578

19 Measurement of Glucose Diffusion Coefficients in Human Tissues 587
Alexey N. Bashkatov, Elina A. Genina and Valery V. Tuchin
19.1 Introduction ................................................................. 588
19.2 Spectroscopic Methods .................................................. 589
19.3 Photoacoustic Technique .............................................. 596
19.4 Use of Radioactive Labels for Detecting Matter Flux .......................................................... 598
19.5 Light Scattering Measurements ........................................ 600
Table of Contents

19.5.1 Spectrophotometry ........................................ 600
19.5.2 OCT and interferometry .................................. 610
19.6 Conclusion .................................................. 612

20 Monitoring of Glucose Diffusion in Epithelial Tissues with Optical Coherence Tomography 623
Kirill V. Larin and Valery V. Tuchin
20.1 Introduction .................................................. 624
20.2 Basic Theories of Glucose-Induced Changes of Tissue Optical Properties ..................... 627
20.3 Experimental Results ........................................ 630
  20.3.1 Materials and methods .................................. 630
  20.3.2 Quantification of molecular diffusion in ocular tissues (cornea and sclera) in vitro ........ 632
  20.3.3 Quantification of glucose diffusion in skin in vitro .............................................. 636
  20.3.4 Quantification of glucose diffusion in skin in vivo .............................................. 637
  20.3.5 Quantification of glucose diffusion in healthy and diseased aortas in vitro ............ 637
  20.3.6 Comparative studies for assessment of molecular diffusion with OCT and histology ...... 640
  20.3.7 Assessment of optical clearing of ocular tissues with OCT .................................... 642
  20.3.8 Depth-resolved assessment of glucose diffusion in tissues ..................................... 643

21 Glucose-Induced Optical Clearing Effects in Tissues and Blood 657
Elina A. Genina, Alexey N. Bashkatov and Valery V. Tuchin
21.1 Introduction .................................................. 658
21.2 Structure and Optical Properties of Fibrous Tissues and Blood .................................... 659
  21.2.1 Structure, physical and optical properties of fibrous tissues .................................. 659
  21.2.2 Structure, physical and optical properties of skin ................................................. 660
  21.2.3 Optical model of fibrous tissue .............................................................................. 661
  21.2.4 Structure, physical and optical properties of blood .............................................. 663
  21.2.5 Optical model of blood ......................................................................................... 664
21.3 Glucose-Induced Optical Clearing Effects in Tissues ......................................................... 666
  21.3.1 Mechanisms of optical immersion clearing ......................................................... 666
  21.3.2 Optical clearing of fibrous tissues ........................................................................... 667
  21.3.3 Optical clearing of skin ........................................................................................... 672
21.4 Glucose-Induced Optical Clearing Effects in Blood and Cellular Structures .................... 679
  21.4.1 Optical clearing of blood ....................................................................................... 679
  21.4.2 Time-domain and frequency-domain measurements ............................................. 682
  21.4.3 Experimental results ............................................................................................. 682
21.5 Conclusion ......................................................... 683