

Contents

Introduction and objectives	XV
1 Glucose Metabolism and Diabetes Mellitus	1
1.1 Introduction to glucose metabolism	2
1.1.1 Endocrine Regulation of Glucose Metabolism	2
1.2 Diabetes Mellitus: definition and history	6
1.2.1 Brief history of the disease	7
1.2.2 Types of Diabetes	9
1.3 DM1 and complications of the disease	10
1.4 Simulating in DM1	14
1.4.1 Hovorka's group simulator [70, 174]	16
1.4.2 UVa Simulator [87, 99, 38, 37]	20
1.5 Conclusions	25
2 Glucose Control in Type 1 Diabetes	27
2.1 Metabolic control monitoring	28
2.2 Insulin administration	31
2.2.1 Administration devices	32
2.3 Open-loop glucose control in type 1 diabetes: intensive insulin therapy	35
2.3.1 Intensive insulin therapy: MDI and CSII	36
2.4 Closed-loop glucose control in type 1 diabetes: Artificial Pancreas	40
2.4.1 Main Challenges	43
2.4.2 Artificial pancreas nowadays	46
2.5 Conclusions	54

3 Open-loop Proposal: Combining basal-bolus insulin infusion for tight postprandial glucose control	55
3.1 Introduction	56
3.2 Theoretical framework: Interval Analysis and Set Inversion	58
3.3 Set-Inversion-Based prandial insulin delivery	61
3.3.1 Output of the algorithm: best basal-bolus combination	65
3.4 <i>In silico</i> evaluation	69
3.4.1 Patient's model identification	71
3.4.2 Metrics used in the <i>in silico</i> evaluation	76
3.4.3 Results of the <i>in silico</i> evaluation	77
3.4.4 Discussion of the <i>in silico</i> evaluation	81
3.5 Clinical validation	87
3.5.1 Characteristics of the study	88
3.5.2 Metrics used and results of the clinical validation	89
3.5.3 Discussion of the clinical validation	90
3.6 Conclusions	92
4 Closed loop strategy: A reference conditioning method for the reduction of hypoglycemia	95
4.1 Introduction	96
4.2 Theoretical framework	99
4.2.1 Invariance Control	99
4.2.2 Finite-time invariance achievement via Sliding Mode Reference Conditioning	101
4.3 Safety auxiliary feedback element (SAFE) in diabetes control .	103
4.3.1 Basics of the algorithm	103
4.3.2 Robustness and fault-tolerance properties	107
4.3.3 SM establishment on safety <i>IOB</i> constraints	109
4.3.4 <i>IOB</i> constraints definition	110
4.4 Simulations and results	112
4.4.1 SAFE algorithm simulations illustrating robustness . .	112
4.4.2 In-silico evaluation using UVA simulator	115
4.5 Conclusions	121

5 Extending SAFE to improve its performance against variability	123
5.1 Theoretical framework	124
5.1.1 Monotonicity analysis	125
5.2 Interval version of SAFE	129
5.3 Simulations and results	130
5.4 Conclusions	134
6 Conclusions	137
6.1 Publications	139
References	143