TABLE OF CONTENTS

Page

I Thesis scope and objectives **1**

1 Diabetes and the artificial pancreas **2**
1.1 Glucose regulation 2
1.1.1 Diabetes overview 4
1.1.2 Types of diabetes 5
1.1.3 Diabetes complications 7
1.1.4 Insulin therapy in type 1 diabetes 8
1.1.5 Challenges to glycemic control 10
1.2 Closed-loop glucose control in type 1 diabetes 13
1.2.1 The artificial pancreas 15
1.2.2 State of development 19

2 Thesis objectives **21**
2.1 Glucose prediction in the artificial pancreas 21
2.2 General objective 22
2.3 Specific objectives 22

II State of the art **25**

3 Glucose prediction in type 1 diabetes **26**
3.1 Challenges of blood glucose prediction 26
3.1.1 Inter- and intra-individual variability 27
3.1.2 Postprandial response 29
3.1.3 Exercise response 30
3.2 Categories of prediction models 32
3.3 Physiological models 36
3.3.1 Minimal model based approaches 36
3.3.2 Medium complexity models 38
3.3.3 Maximal models 41
3.4 Data-driven models 43

3.4.1 AR and ARMA models . . . 43
3.4.2 ARX and ARMAX models . . . 44
3.4.3 Other empirical models . . . 45
3.5 Hybrid models . . . 47
3.6 Prediction performance analysis . . . 49

4 Stochastic time series modeling 52
4.1 Preliminary concepts . . . 52
4.2 Linear time series models . . . 59
4.2.1 Autoregressive (AR) process . . . 60
4.2.2 Moving average (MA) process . . . 63
4.2.3 Mixed autoregressive moving average (ARMA) processes 64
4.2.4 Autoregressive integrated moving average (ARIMA) processes . . . 65
4.2.5 Seasonal ARIMA processes . . . 66
4.2.6 Processes with exogenous variables . . . 66
4.3 The strategy of building models . . . 69
4.3.1 Stationarity test . . . 69
4.3.2 Model identification . . . 71
4.3.3 Model estimation . . . 74
4.3.4 Diagnostic checking . . . 76
4.3.5 Forecasting . . . 78

5 Clustering time series 81
5.1 Clustering time series data . . . 81
5.2 Similarity and distance measures . . . 84
5.2.1 Similarity in time . . . 84
5.2.2 Similarity in shape . . . 85
5.2.3 Structural similarity . . . 87
5.3 Approaches to time series clustering . . . 87
5.3.1 Raw-data-based approaches . . . 88
5.3.2 Feature-based approaches . . . 88
5.3.3 Model-based approaches . . . 89
5.4 Time series clustering algorithms . . . 89
5.4.1 Hierarchical clustering . . . 90
5.4.2 Partitional clustering . . . 93
5.4.3 Cluster validity indices . . . 98
5.5 Clustering and local modeling . . . 104
5.5.1 Why local modeling? . . . 104
5.5.2 Local modeling techniques . . . 105
5.6 Clustering applications in type 1 diabetes . . . 108

III Contributions **111**

6 Seasonality and glucose prediction **112**
6.1 Rationale . . . 112
6.2 Research Design and Methods . . . 113
6.2.1 Clinical dataset . . . 113
6.2.2 Data pre-processing . . . 116
6.2.3 SARIMA and SARIMAX models . . . 118
6.2.4 Identification procedure . . . 119
6.3 Results . . . 120
6.3.1 Without exogenous variables . . . 120
6.3.2 With exogenous variables . . . 122
6.4 Conclusions and margins for further improvement . . . 124

7 Seasonal local models **128**
7.1 Rationale . . . 128
7.2 Research Design and Methods . . . 129
7.2.1 Details of procedures . . . 129
7.2.2 Meal protocol . . . 130
7.2.3 Exercise protocol . . . 130
7.2.4 Closed-loop system . . . 131
7.2.5 Statistical procedures . . . 131
7.2.6 FCM clustering algorithm . . . 132
7.2.7 Seasonal models with exogenous signals . . . 133
7.2.8 Models integration . . . 134
7.2.9 Validation procedure . . . 135
7.3 Results . . . 135
7.3.1 Data clustering . . . 135
7.3.2 Model identification . . . 140
7.4 Conclusions and margins for further improvement . . . 145

8 Seasonality in free-living conditions **147**
8.1 Rationale . . . 147
8.2 Research Design and Methods . . . 148
8.2.1 Data overview . . . 148
8.2.2 Data preprocessing . . . 149
8.2.3 Time series clustering algorithm . . . 149
8.2.4 SARIMA local models integration for online glucose prediction . . . 151
8.2.5 Supervision system and abnormal states detection . . . 151
8.2.6 Validation procedure . . . 153
8.3 Results . . . 154
8.3.1 Time series building . . . 156
8.3.2 Data clustering . . . 156

8.3.3 Model identification 156
8.3.4 Online forecasting validation 159
8.3.5 Supervision system validation and abnormal states detection 160
8.4 Conclusions and margins for further improvement 166

9 Conclusions and Future work **169**
9.1 Conclusions 169
9.2 Future work 172
9.3 Publications 173
9.3.1 Journal papers 173
9.3.2 Conference abstracts and posters 173

A Clarke error grid analysis **176**
A.1 Clarke error grid analysis 176
A.2 Continuous glucose error grid analysis 177