MODELING GLUCOSE-INSULIN DYNAMICS AND AUTOMATED BLOOD GLUCOSE REGULATION IN PATIENTS WITH TYPE 1 DIABETES

BY
MERIYAN ORUKLU

Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemical and Biological Engineering in the Graduate College of the Illinois Institute of Technology

Approved
Advisor

Chicago, Illinois
December 2012
ACKNOWLEDGMENT

I dedicate this Doctoral thesis to my little angel, Lara, who brightens up my days with her smile.

I am most grateful to my husband, Erdal Oruklu, for his constant love and endless encouragements when I needed it the most. I would also like to thank my parents, Gulten Eren and Ruksen Eren, for their love and unconditional support during this process and over the years.

I would like to acknowledge the support, guidance and expertise that I received throughout this project from my supervisor, Dr. Ali Cinar. He showed me how the hard work is actually rewarded, and because of him I know what values to teach my little daughter. Finally, I would like to thank Dr. Lauretta Quinn and Dr. Derrick Rollins for providing the data used in this project.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGEMENT</td>
<td>iii</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>vii</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>xi</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>xii</td>
</tr>
<tr>
<td>CHAPTER</td>
<td></td>
</tr>
<tr>
<td>1. INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>1.1. Characteristics of Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>1.2. Blood Glucose Regulation Problem Statement</td>
<td>3</td>
</tr>
<tr>
<td>1.3. Current Insulin Therapies</td>
<td>4</td>
</tr>
<tr>
<td>1.4. Future of Diabetes Management</td>
<td>6</td>
</tr>
<tr>
<td>2. RESEARCH OBJECTIVES</td>
<td>12</td>
</tr>
<tr>
<td>3. LITERATURE REVIEW</td>
<td>18</td>
</tr>
<tr>
<td>3.1. Review of Existing Approaches to Modeling Glucose-Insulin Dynamics</td>
<td>18</td>
</tr>
<tr>
<td>3.2. Review of Existing Approaches to Closed-Loop Blood Glucose Regulation</td>
<td>29</td>
</tr>
<tr>
<td>3.3. Shortcomings of Existing Modeling and Control Approaches</td>
<td>36</td>
</tr>
<tr>
<td>4. MODELING ALGORITHM FOR ESTIMATION OF FUTURE GLUCOSE CONCENTRATIONS</td>
<td>40</td>
</tr>
<tr>
<td>4.1. Challenges</td>
<td>40</td>
</tr>
<tr>
<td>4.2. Time-Series Models</td>
<td>41</td>
</tr>
<tr>
<td>4.3. Criterion for Model Type and Order Selection</td>
<td>47</td>
</tr>
<tr>
<td>4.4. Identification of Model Parameters</td>
<td>48</td>
</tr>
<tr>
<td>4.5. Change Detection</td>
<td>50</td>
</tr>
<tr>
<td>4.6. n-steps-ahead Prediction</td>
<td>52</td>
</tr>
<tr>
<td>4.7. Prediction Performance Analyses</td>
<td>53</td>
</tr>
<tr>
<td>5. CLOSED-LOOP CONTROL ALGORITHM FOR BLOOD GLUCOSE REGULATION</td>
<td>57</td>
</tr>
<tr>
<td>5.1. Challenges</td>
<td>57</td>
</tr>
<tr>
<td>5.2. Delay Compensators</td>
<td>59</td>
</tr>
<tr>
<td>5.3. Model</td>
<td>61</td>
</tr>
</tbody>
</table>
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Types of Insulin</td>
<td>6</td>
</tr>
<tr>
<td>6.1</td>
<td>AIC Values for AR and MA Models with Various Model Orders</td>
<td>76</td>
</tr>
<tr>
<td>6.2</td>
<td>AIC Values for ARMA($n_A, n_C$) Model with Various Model Orders</td>
<td>77</td>
</tr>
<tr>
<td>6.3</td>
<td>Model Parameter and Glucose Prediction Error Metrics for Patients Represented in Figure 6.1</td>
<td>79</td>
</tr>
<tr>
<td>6.4</td>
<td>Prediction Performances for Several PH Values Using Time-Invariant Models</td>
<td>80</td>
</tr>
<tr>
<td>6.5</td>
<td>Error Metrics for Patients Represented in Figure 6.2</td>
<td>83</td>
</tr>
<tr>
<td>6.6</td>
<td>Prediction Performances for Several PH Values Using the Recursive Algorithm with and without the Change Detection Strategy</td>
<td>87</td>
</tr>
<tr>
<td>6.7</td>
<td>Error Matrix of CG-EGA for Predicted Glucose Values with $PH = 6$ for Study Group B</td>
<td>89</td>
</tr>
<tr>
<td>6.8</td>
<td>Error Metrics for Patients Represented in Figure 6.6</td>
<td>90</td>
</tr>
<tr>
<td>7.1</td>
<td>Closed-Loop Performance for Case Scenario A</td>
<td>108</td>
</tr>
<tr>
<td>7.2</td>
<td>Closed-Loop Performance for Case Scenario B</td>
<td>115</td>
</tr>
<tr>
<td>8.1</td>
<td>Prediction performance (30 min ahead)</td>
<td>130</td>
</tr>
<tr>
<td>9.1</td>
<td>Glucose regulation during the two closed-loop experiments</td>
<td>152</td>
</tr>
<tr>
<td>9.2</td>
<td>Glucose regulation during the two closed-loop experiments</td>
<td>156</td>
</tr>
<tr>
<td>B.1</td>
<td>Flow Rates</td>
<td>171</td>
</tr>
<tr>
<td>B.2</td>
<td>Volumes</td>
<td>172</td>
</tr>
<tr>
<td>B.3</td>
<td>Model Parameters</td>
<td>173</td>
</tr>
<tr>
<td>B.4</td>
<td>Model Parameters</td>
<td>178</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>1.1</td>
<td>Components of a typical blood glucose meter [1].</td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td>(a) First Insulin Pump [2] (b) MiniMed Paradigm System [3]: (A) Insulin Pump displays continuous glucose measurements, (B) Infusion Set, (C) Glucose Sensor, and (D) MiniLink REAL-Time Transmitter.</td>
<td></td>
</tr>
<tr>
<td>2.1</td>
<td>Block diagram of an artificial pancreas.</td>
<td></td>
</tr>
<tr>
<td>4.1</td>
<td>Scatter plots for CG-EGA. (a) Point-EGA, and (b) Rate-EGA.</td>
<td></td>
</tr>
<tr>
<td>5.1</td>
<td>Block diagram of the proposed closed-loop strategy when blood glucose concentration is estimated from subcutaneous glucose measurements.</td>
<td></td>
</tr>
<tr>
<td>5.2</td>
<td>Smith predictor structure used for (a) GPC strategy, and (b) LQC strategy.</td>
<td></td>
</tr>
<tr>
<td>5.3</td>
<td>Time-varying reference trajectory for glucose concentration.</td>
<td></td>
</tr>
<tr>
<td>6.1</td>
<td>Prediction of glucose concentrations with time-invariant models for a representative (a) healthy subject, (b) glucose-intolerant subject, and (c) subject with diabetes of study group A, with PH = 2 steps.</td>
<td></td>
</tr>
<tr>
<td>6.2</td>
<td>Glucose estimation with time-invariant ARMA(3,1) model and pure-lagged (i.e., zero-order-hold) glucose data, for a representative (a) healthy subject, (b) glucose-intolerant subject, and (c) subject with diabetes of study group A.</td>
<td></td>
</tr>
<tr>
<td>6.3</td>
<td>Prediction of glucose concentrations with the recursive algorithm for a representative (a) healthy subject, and (b) subject with diabetes of study group B.</td>
<td></td>
</tr>
<tr>
<td>6.4</td>
<td>Variation in model parameters (i.e, $\hat{a}_1$, $\hat{a}_2$ and $\hat{c}_1$ for the ARMA(2,1) model) for a representative healthy subject of study group B. Predicted glucose concentrations are for PH=6 steps (i.e., 30 min). The representative subject is the same as in Figure 6.3(a).</td>
<td></td>
</tr>
<tr>
<td>6.5</td>
<td>Variation in model parameters (i.e, $\hat{a}_1$, $\hat{a}_2$ and $\hat{c}_1$ for the ARMA(2,1) model) for a representative subject with diabetes of study group B. Predicted glucose concentrations are for PH=6 steps (i.e., 30 min). The Representative subject is the same as in Figure 6.3(b).</td>
<td></td>
</tr>
</tbody>
</table>
6.6 Glucose estimation with the proposed recursive algorithm and pure-lagged (zero-order-hold) glucose data, for a representative (a) healthy subject, and (b) subject with diabetes of study group B. .......................... 93

7.1 Closed-loop glucose regulation with GPC in response to Case Scenario A (Section 7.2) with 70% insulin reduction. Results are for a virtual subject simulated with GlucoSim model, (a) blood glucose concentration for $\tau = 5, 10$ and $20 \text{ min}$, and (b)-(d) subcutaneous insulin infusion for $\tau = 5, 10$ and $20 \text{ min}$, respectively. .......................... 104

7.2 Closed-loop glucose regulation with LQC in response to Case Scenario A (Section 7.2) with 70% insulin reduction. Results are for a virtual subject simulated with GlucoSim model, (a) blood glucose concentration for $\tau = 5, 10$ and $20 \text{ min}$, and (b)-(d) subcutaneous insulin infusion for $\tau = 5, 10$ and $20 \text{ min}$, respectively. .......................... 105

7.3 Closed-loop glucose regulation with GPC in response to Case Scenario A (Section 7.2) with 70% insulin reduction. Results are for $\tau = 5 \text{ min}$ and a virtual subject simulated with Hovorka and GlucoSim models, (a) blood glucose concentration, and (b)-(c) subcutaneous insulin infusion for GlucoSim and Hovorka models, respectively. 110

7.4 Closed-loop glucose regulation with LQC in response to Case Scenario A (Section 7.2) with 70% insulin reduction. Results are for $\tau = 5 \text{ min}$ and a virtual subject simulated with Hovorka and GlucoSim models, (a) blood glucose concentration, and (b)-(c) subcutaneous insulin infusion for GlucoSim and Hovorka models, respectively. 111

7.5 Closed-loop glucose regulation with GPC and LQC in response to Case Scenario B (Section 7.2) with 70% insulin reduction. Results are for $\tau = 5 \text{ min}$ and a virtual subject simulated with GlucoSim model, (a) blood glucose concentration, and (b)-(c) subcutaneous insulin infusion with GPC and LQC, respectively. .......................... 113

7.6 Closed-loop glucose regulation with GPC and LQC in response to Case Scenario B (Section 7.2) with 70% insulin reduction. Results are for $\tau = 5 \text{ min}$ and a virtual subject simulated with Hovorka model, (a) blood glucose concentration, and (b)-(c) subcutaneous insulin infusion with GPC and LQC, respectively. .......................... 114

8.1 SenseWear Pro3 Armband by BobyMedia Inc. [4] .................. 124

8.2 Glucose prediction with the multivariate and the univariate algorithms. .......................... 126

8.3 Energy expenditure signal from the SenseWear armband used for the multivariate glucose predictions in Figure 8.2. .......................... 127
8.4 Average longitudinal acceleration signal from the SenseWear armband used for the multivariate glucose predictions in Figure 8.2. . 128
8.5 Heat flux signal from the SenseWear armband used for the multivariate glucose predictions in Figure 8.2. . . . . . . . . . . . . . 128
8.6 Galvanic skin response signal from the SenseWear armband used for the multivariate glucose predictions in Figure 8.2. . . . . . . . . 129
8.7 Near-body temperature signal from the SenseWear armband used for the multivariate glucose predictions in Figure 8.2. . . . . . . . 129
8.8 Early hypoglycemic alarms with the multivariate algorithm for 30 min ahead prediction and 60 mg/dl hypoglycemia threshold. . . . . . . . . . . . . . 132
8.9 ROC curves for prediction horizons of 15, 30 and 45 min (i.e., $PH = 3, 6, \text{ and } 9$ steps). Hypoglycemia thresholds are increased at 10 mg/dl intervals in the range of 60-120 mg/dl . . . . . . . . . . . . 133
9.1 Block diagram of the proposed multivariate closed-loop strategy. . 137
9.2 Glucose concentrations during the first closed-loop experiment. . . 146
9.3 Basal insulin infusion rates commanded by the multivariate control algorithm during the first closed-loop experiment. . . . . . . . . . 146
9.4 Energy expenditure measured by the armband and used by the control algorithm during the first closed-loop experiment. . . . . . . . . . . . . . 148
9.5 Average longitudinal acceleration measured by the armband and used by the control algorithm during the first closed-loop experiment. 148
9.6 Heat flux measured by the armband and used by the control algorithm during the first closed-loop experiment. . . . . . . . . . . . . . 149
9.7 Galvanic skin response measured by the armband and used by the control algorithm during the first closed-loop experiment. . . . . . . . . . . . . . 149
9.8 Near-body temperature measured by the armband and used by the control algorithm during the first closed-loop experiment. . . . . . . . . . . . . . 150
9.9 Glucose concentrations during the second closed-loop experiment. . 151
9.10 Basal insulin infusion rates commanded by the multivariate control algorithm during the second closed-loop experiment. . . . . . . . . . . . . . 151
9.11 Energy expenditure measured by the armband and used by the control algorithm during the second closed-loop experiment. . . . . . . . . . . . . . 153
<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.12</td>
<td>Average longitudinal acceleration measured by the armband and used by the control algorithm during the second closed-loop experiment.</td>
<td>153</td>
</tr>
<tr>
<td>9.13</td>
<td>Heat flux measured by the armband and used by the control algorithm during the second closed-loop experiment.</td>
<td>154</td>
</tr>
<tr>
<td>9.14</td>
<td>Galvanic skin response measured by the armband and used by the control algorithm during the second closed-loop experiment.</td>
<td>154</td>
</tr>
<tr>
<td>9.15</td>
<td>Near-body temperature measured by the armband and used by the control algorithm during the second closed-loop experiment.</td>
<td>155</td>
</tr>
<tr>
<td>B.1</td>
<td>Pharmacokinetic diagram of the glucose model [5].</td>
<td>166</td>
</tr>
<tr>
<td>B.2</td>
<td>Pharmacokinetic diagram of the insulin model [5].</td>
<td>169</td>
</tr>
<tr>
<td>B.3</td>
<td>Compartmental diagram of glucose, insulin and insulin action sub-systems [6].</td>
<td>175</td>
</tr>
</tbody>
</table>
Estimation of future glucose concentrations is a crucial task for diabetes management. Predicted glucose values can be used for early hypoglycemic/hyperglycemic alarms or for adjustment of insulin amount/rate. In the first part of this thesis, reliable subject-specific glucose concentration prediction models are developed using a patient’s continuous glucose monitoring (CGM) data. CGM technologies provide glucose readings at a high frequency and consequently detailed insight into a patient’s glucose variation.

Time-series analyses are utilized to develop low-order linear models from a patient’s own CGM data. Glucose prediction models are integrated with recursive identification and change detection methods, which enable dynamical adaptation of the model to inter-/intra-subject variability and glycemic disturbances. Two separate patient data sets collected under hospitalized (disturbance-free) and normal daily life conditions are used to validate the univariate glucose prediction algorithm developed. Prediction performance is evaluated in terms of prediction error metrics and Clarke error grid analysis (CG-EGA).

The long-term complications of diabetes can be reduced by controlling the blood glucose concentrations within normoglycemic limits. In the second part of this thesis, the subject-specific modeling algorithm developed in part one is integrated with a control algorithm for closing the glucose regulation loop for patients with type 1 diabetes. An adaptive control algorithm is developed to keep a patient’s glucose concentrations within normoglycemic range and dynamically respond to glycemic challenges with automated subcutaneous insulin infusion. A model-based control strategy is used to calculate the required insulin infusion rate, while the model parameters are recursively identified at each sampling step. The closed-loop algorithm is designed for the subcutaneous route for both glucose sensing and insulin delivery.
It accounts for the slow insulin absorption from the adipose tissue and the time-delay between blood and subcutaneous glucose concentrations. The performance of the control algorithm developed is demonstrated on two simulated patient populations to provide effective blood glucose regulation in response to multiple meal challenges with a simultaneous challenge on a patient’s insulin sensitivity.

Physical activity and emotional stimuli such as stress are known to have a significant effect on a patient’s whole-body fuel metabolism. In the third part of this thesis, the univariate time-series models developed from recent glucose concentration history are extended to include additional information on a patient’s physical and emotional condition. Physiological measurements from a multi-sensor body monitor are used to supplement a patient’s CGM data and develop multivariate glucose prediction models. The prediction performance of the multivariate algorithm developed is evaluated on data collected from patients with type 2 diabetes, and a real life implementation of the algorithm is demonstrated for early (i.e., 30 min in advance) hypoglycemia detection.

Finally, the control algorithm developed in part two is extended to utilize the glucose profiles predicted by the multivariate patient model. The multivariate closed-loop algorithm is tested with two clinical experiments performed on a patient with type 1 diabetes during a high intensity exercise followed by a carbohydrate-rich meal challenge. The algorithm acquires the patient’s CGM and armband (body monitor) data every 10 min, and accordingly calculates the required basal insulin infusion rate. Insulin is administered in a fully automated manner without any food or activity announcements (e.g., no information on meal/exercise size or time).

None of the algorithms developed in this thesis require any patient specific tailoring or prior experimental data before implementation. They are also designed to function in a fully automated manner and do not require any disturbance announce-
ments or manual inputs. Therefore, they are good candidates for installation on a portable ambulatory device used in a patient’s home environment for his/her diabetes management.
CHAPTER 1
INTRODUCTION

The ultimate objective of this thesis is to develop reliable subject-specific glucose prediction models and a model-based control algorithm that regulates a subject’s blood glucose levels with exogenous administration of insulin. A fully automated system that eliminates any patient intervention is developed to improve the management and control of diabetes for insulin dependent patients. The algorithms developed use real-time measurements from a patient’s continuous glucose monitoring (CGM) sensor and a multi-sensor body monitor, and do not require prior experimental data or subject specific tailoring before implementation.

This chapter provides the background information necessary to understand the characteristics of diabetes and the glucose control problem that patients with diabetes face. It also describes current insulin therapies and the future of diabetes management. Chapter 2 discusses the research objectives of this thesis, and Chapter 3 provides a literature review of the approaches for glucose modeling and closed-loop glucose regulation. Chapters 4 and 5 introduce the individual components of the modeling and the control algorithms developed, respectively. In Chapters 6 and 7, the algorithms developed are implemented for the univariate case where only CGM sensor data is utilized. In Chapters 8 and 9, results for the multivariate case are demonstrated where CGM sensor data and additional physiological measurements from a multi-sensor body monitor are utilized. Finally, Chapter 10 concludes with a general discussion of the proposed algorithms and their efficiency.

1.1 Characteristics of Diabetes

Diabetes is a disease characterized by deficiency of insulin secretion or deficiency of the body to respond to insulin normally (insulin resistance), or both. This
imbalance of insulin, a hormone produced by the beta-cells of the islets of Langerhans in the pancreas, impairs the metabolism of glucose and other nutrients in the bloodstream. Glucose homeostasis in healthy person is a balance between glucose production by the liver and glucose utilization by tissues. Insulin is effective on returning elevated blood glucose levels back to normal by promoting the uptake of glucose into tissues as fuel for energy and its storage for future use. In contrast, insulin release is suppressed during low blood glucose conditions to promote glucose production from the liver.

Metabolic imbalance in patients with diabetes results in very high blood glucose concentrations which in long-term can lead to deterioration in various tissues and their functioning. There are two main types of diabetes: type 1 and type 2 diabetes. In patients with type 1 diabetes, pancreatic beta-cells are destroyed by the autoimmune process and therefore patients are not able to produce insulin and are totally dependent on exogenous insulin to regulate their blood glucose levels. Unlike type 1 diabetes, in type 2 diabetes the body produces insulin, however, is not able to recognize and respond to it properly (i.e., insulin-resistance) which initially leads to increased insulin secretion by pancreas. Elevated insulin release causes deterioration of beta-cells over time and consequently reduction in insulin levels.

Therapies conducted for management with type 1 and type 2 diabetes are also different. All patients with type 1 require exogenous insulin that is administered by 3-5 insulin injections per day or by a manual insulin-pump. Patients with type 1 diabetes are also recommended to follow a strict diet and sometimes an exercise routine to eliminate randomness in the glycemic disturbances encountered during daily life, in order to make management with the disease easier. In contrast, only 27% of the patients with type 2 diabetes administer insulin [7], with the majority of the patients using oral medications that aim to reduce insulin resistance and stimulate
endogenous insulin production. At the early stages of the disease, type 2 diabetes can be preventable with prescribed diet and exercise program, while type 1 diabetes currently remains as an incurable life-long disease.

Diabetes affected 171 million people in year 2000 worldwide [8]. Assuming obesity levels to remain constant, this number is projected to increase to 366 million by 2030 [8]. Type 1 diabetes accounts for approximately 10% of all the diabetes cases, and it usually develops in children or adults under age 30. Type 2 diabetes traditionally is known to affect adults over age 40, however, with the rise in prevalence of obesity in youth, it is increasingly diagnosed among younger individuals and children. As the number of younger individuals who will live longer with the disease increases, more patients will develop severe beta-cell dysfunction and require insulin therapy.

Persistent high glucose level (i.e., hyperglycemia) in diabetes is the major cause of severe long-term complications that include diabetic ketoacidosis, cardiovascular diseases, kidney failure, diabetic retinopathy, diabetic neuropathy, and foot ulcers. These complications reduce the overall life expectancy of the patient by 25% [9]. In the United States, diabetes has been reported as the seventh leading cause of death in 2006, and the estimated total cost of the disease has been $174 billion for 2007 [7]. The diabetes control and complications trial (DCCT) [10] and the United Kingdom prospective diabetes study (UKPDS) [11] have demonstrated that keeping blood glucose concentrations within tight control significantly delays the onset and slows the progression of diabetic complications, and therefore can reduce the morbidity and mortality rates of the disease.

1.2 Blood Glucose Regulation Problem Statement

In the absence of glucose, the body can shift to utilization of fats and proteins as fuel for energy. However, glucose is the only nutrient that the brain can use. Normal
functioning of the central nervous system depends on continuous supply of glucose since the neurons are not able to store glucose. For blood glucose concentrations below 40 mg/dl (i.e., severe hypoglycemia), severe impairment in the nervous system has the potential to lead to seizure, diabetic coma and eventually death [12]. On the other hand, avoiding elevated glucose concentrations is equally important, since hyperglycemia leads to rise in osmotic pressure causing cellular dehydration, and loss of glucose in the urine (threshold ≈ 180 mg/dl glucose) causing osmotic diuresis in the kidneys [13]. Persistent hyperglycemia is also known as the major cause for the diabetic complications. Therefore, maintenance of normoglycemia is highly crucial. Studies of [10] and [11] have demonstrated the significance of achieving glucose levels as close to those observed in healthy subjects as possible, in order to reduce the risk of long-term complications associated with diabetes and the morbidity and mortality rates of the disease.

In healthy subjects, blood glucose concentrations are regulated within tight limits. This range is 70-90 mg/dl of glucose during fasting conditions. Conversely, following a meal, glucose concentrations increase to 120-160 mg/dl depending on the meal size, however normalization to fasting levels is rapidly achieved (usually within 2-3 h). In diabetes, with the deficiency of insulin, glucose levels cannot be reduced after a meal, and blood glucose concentrations as high as 300-400 mg/dl can be observed if exogenous insulin is not administered. Similarly, fasting glucose concentrations can be as high as 150-250 mg/dl for untreated patients.

In summary, blood glucose control problem in patients with diabetes involves the prevention of hyperglycemia, and the minimization of time-average of blood glucose variation while avoiding hypoglycemia.

1.3 Current Insulin Therapies
Currently, there are two major insulin regimens prescribed by the clinicians for patients with diabetes. These are known as conventional and intensive insulin therapies. In the conventional insulin therapy, patients take one to three fixed and predefined doses of insulin every day. Number of injections, dose, insulin type, and injection timings (e.g., before breakfast, before dinner and/or at bedtime) are determined by the clinician based on glycemic disturbances of a typical day of the patient. With this therapy, patients are required to follow a rigid life style by eating approximately the same amount of food at the same time and maintaining the same activity levels every day. On the other hand, the intensive insulin therapy separates the meal-related and basal insulin types and doses, in order to more closely mimic the normal physiological insulin release, and at the same time provide more flexibility in patients’ daily lives. In the intensive insulin therapy, the number of injections is increased to three to five insulin administrations per day. Bolus dose of regular- or rapid-acting insulin is taken before each meal, and basal insulin (e.g., long-acting) is usually administered once daily at bedtime to achieve target fasting blood glucose concentrations. Patients are also required to test their blood glucose levels before each injection for adjusting the insulin dose.

The DCCT [10] and UKPDS [11] studies have demonstrated that compared to conventional insulin therapy, the intensive therapy is significantly better at normalizing blood glucose levels of insulin-dependent patients. In addition, with the recent discovery of rapid-acting insulin analogs (e.g., insulin lispro, Humalog, by Eli Lilly in 1996 and insulin aspart, Novolog, by Novo Nordisk in 2001), intensive insulin therapy became the standard of care, especially for patients with type 1 diabetes. Rapid-acting insulin is taken 10-15 min before starting a meal (see Table 1.1), and therefore provides more flexibility with meal timings. Compared to other insulin types, it also more closely mimics the normal physiological insulin response to a meal challenge as displayed in Table 1.1.
Table 1.1. Types of Insulin

<table>
<thead>
<tr>
<th>Type of Insulin</th>
<th>Rapid-Acting</th>
<th>Short-Acting</th>
<th>Intermediate-Acting</th>
<th>Long-Acting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>5-15 min</td>
<td>30-60 min</td>
<td>2-4 h</td>
<td>2-4 h</td>
</tr>
<tr>
<td>Peak</td>
<td>45-90 min</td>
<td>2-3 h</td>
<td>4-10 h</td>
<td>No clear peak</td>
</tr>
<tr>
<td>Duration</td>
<td>3-4 h</td>
<td>5-8 h</td>
<td>10-16 h</td>
<td>20 h or more</td>
</tr>
<tr>
<td>Role in Diabetes Management</td>
<td>Used generally as bolus insulin to cover meals.</td>
<td>Used generally as bolus insulin to cover meals.</td>
<td>Used as basal insulin to cover between-meal and overnight blood glucose levels.</td>
<td>Used as basal insulin to cover between-meal and overnight blood glucose levels.</td>
</tr>
<tr>
<td></td>
<td>Should be taken 10-15 min before meals.</td>
<td>Should be taken 30-45 min before meals.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Intensive insulin therapy gives the patients the chance to adjust their bolus (i.e., meal-related) insulin dose based on their premeal blood glucose fingerstick test, estimated carbohydrate content of the meal, and anticipated postmeal activity levels. Even tough the patients have more flexibility with their meal size and timings, they still have to follow some guidelines provided by their clinicians when fine-tuning their insulin or daily activity schedules. For full flexibility in daily life, highly individualized insulin regimen and guidelines for proper insulin adjustment that fits a patient’s lifestyle are required. Patient education also plays an important role in achieving good blood glucose regulation with the intensive insulin therapy.

Success rate at achieving normoglycemia with the current insulin therapies has been very low. The main reasons for this remain to be the changing daily life conditions such as stress, illness, or activity levels, and the high inter-patient variation in glucose metabolism. Even with the more individualized intensive therapy, three-fold increase in severe hypoglycemic incidences has been reported compared to conventional therapy [10].

1.4 Future of Diabetes Management
A cure for diabetes would be a treatment that replaces the insulin producing pancreatic beta-cells. Currently, the most promising research directions in this field are the whole pancreas or the isolated pancreatic islet-cell transplantation. Both methods require life-long immunosuppression to prevent rejection of the graft and destruction of the pancreatic islet beta-cells. The severe side effects of the immunosuppressive drugs restrict the use of pancreas transplants on patients who have developed series complications of diabetes [14]. In contrast to pancreas transplant, islet-cell transplantation does not involve a major surgery (e.g., islets are injected to their location) and require a lesser degree of immunosuppression [15]. However, the major limitation for islet-cell transplants is the shortage of human islet supply, as each patient may need 2-3 separate transplants from 2-4 cadaveric donors [16]. There is an extensive research focusing on encapsulation of islet cells with a semipermeable membrane [17]. The encapsulation will protect the cells from the attack of the host immune system, and also increase the islet supply by using islets harvested from animals (e.g., pigs or cows), or from engineered cells (e.g., stem cells).

The number of whole pancreas transplants performed is relatively low, and the islet-cell transplantation studies are still considered in experimental stage. Meanwhile, with the emerging new technologies in glucose monitoring and insulin infusion pumps, a fully automated closed-loop insulin therapy is more likely to become reality in the near future. Development of such an artificial mechanical pancreas is one of the main objectives of this thesis. A detailed review of the studies in this field is provided in Section 3.2. Therefore, in this section, we will suffice with a brief history on glucose monitoring and insulin pump technologies.

**1.4.1 Glucose Monitoring.** Until the 20th century, diabetes was diagnosed by sampling a patient’s urine. In the 1960s, urine strips were developed for home use. Hypoglycemia and hyperglycemia were indicated with different strip colors. Anton
Hubert Clemens invented the first portable glucose meter, commercialized by Ames Diagnostics. This was a 10 in long device weighting about 3 lb, and was designed for clinical use only. In the 1980s, portable glucose meters for home-use appeared on the market. They allowed for self-monitoring of blood glucose (SMBG) data at home. After 30 years, it is still the most widely used and accepted glucose monitoring technique for fine-tuning daily insulin regimens by patients with diabetes. Figure 1.1 demonstrates the components of a typical glucose meter currently available in the market. Patients need to prick their finger tips with the lancet, and place a drop of blood on the test strip that is inserted to the meter to show the blood glucose concentration on the screen.

SMBG provides only instantaneous blood glucose concentration and does not include any information about the direction or rate of blood glucose change. Therefore, many patients are unable to achieve target levels, even though they test their blood glucose 5-8 times per day.

Recent developments in continuous glucose monitoring (CGM) technology have the potential to revolutionize diabetes management in the near future. The non-invasive or minimally invasive CGM devices measure glucose concentration in the interstitial fluid, and provide discrete glucose concentration data at a high fre-
frequency (e.g., 3-5 min sampling time). They provide more insight not only into a patient’s glucose profile during the day, but also into the rate at which glucose fluctuations occur. However, these devices are not yet widely adopted by clinicians or patients, since several challenges remain to be addressed. Current CGM devices do not eliminate fingerstick measurements, as they require a few calibrations during the day. The current lifetime of the sensor is around 3-7 days. Therefore, patients are required to replace the sensor once or twice a week, which makes monitoring glucose with a CGM device expensive. Review of CGM technologies [18], [19] and the discussion of accuracy and reliability concerns of the current CGM devices [20] are available in the literature.

Development of reliable CGM devices is still an extensively on-going research. It is a common belief that when the limitations with such devices are solved in the near future, the CGM will revolutionize the diabetes management. For instance, such frequent glucose data can be used for development of models predicting future glucose concentrations (see Section 3.1.3, and Chapters 6 and 8), and the predicted glucose levels can be used for early hypoglycemic or hyperglycemic alarms [21] (see Section 8.6), or for closing the loop of blood glucose regulation with an automated insulin pump (see Section 3.2, and Chapters 7 and 9).

1.4.2 Insulin Pumps. The first insulin pump was devised by Arnold Kadish in the early 1960s [22]. It was a bulky device worn on the back as shown in Figure 1.2(a), delivering both insulin and glucagon. It is only in the 1990s that advances in the pump technology led to more user-friendly and significantly smaller pumps. Current insulin pumps deliver rapid-acting insulin continuously through a catheter placed under the skin. They accurately deliver microdoses of insulin, and are enhanced with safety alarms in case of malfunction. Basal insulin is delivered continuously at a constant rate. The patient can program different basal rates through the day and
has to manually enter his/her bolus insulin doses before each meal. Currently, the
most advanced system available in the market is the MiniMed Paradigm (Medtronic
MiniMed, Northridge, CA). It combines a CGM system with an insulin infusion
system into one device as shown in Figure 1.2(b). Even tough insulin regimen/doses
are entered manually by the patients, it is considered as a major step toward the
development of the artificial pancreas.

Apart from the external insulin infusion pumps, there are pumps that are im-
planted within the body. Such pumps provide intravenous or intraperitoneal insulin
infusion which eliminates the time-delays related to slow insulin absorption with ex-
ternal pumps, and therefore, make the blood glucose control problem easier. However, the use of implantable pumps remains very low, due to the invasive methods during implantation, cost, and problems with refilling of these pumps.
CHAPTER 2
RESEARCH OBJECTIVES

In this thesis, a subject-specific modeling algorithm for predicting a patient’s future glucose concentrations and a model-based control algorithm for fully automated blood glucose regulation are developed. The research conducted is partitioned into three separate phases:

- **Phase I:** Development of univariate subject-specific glucose prediction models using real-time continuous glucose monitoring (CGM) data.

- **Phase II:** Development of a closed-loop control algorithm that implements the modeling strategy proposed in Phase I to automatically regulate blood glucose concentrations of patients with type 1 diabetes.

- **Phase III:** (a) Development of multivariate subject-specific glucose prediction models using a patient’s CGM data and physiological measurements from a multi-sensor body monitor. (b) Extension of the blood glucose control algorithm developed in Phase II to utilize the multivariate glucose prediction models for fully automated blood glucose regulation.

Estimation of future glucose concentrations is a crucial task for diabetes management. Predicted glucose values can be used for early hypoglycemic/hyperglycemic alarms or for adjustment of insulin amount/rate. In the first part of this thesis, the goal is to develop univariate empirical models from a subject’s recent CGM history, and use the models developed to predict the subject’s future glucose excursions. This phase involves analyses of CGM glucose concentration data collected from hospitalized and ambulatory patients. CGM technologies provide glucose readings at a high frequency and consequently detailed insight into a subject’s glucose variation.
Glucose-insulin dynamics shows great variability from subject to subject. Metabolic changes caused by stress, illness or changes in insulin sensitivity may also lead to significant variation in glucose-insulin dynamics within the same subject. Therefore, the models developed should be subject-specific and able to adapt and capture inter- and intra-subject variability in the glucose homeostasis. For many modeling strategies, this will require prior experimental data from each patient for off-line tuning of the model parameters, and therefore, may limit the strategy from being implemented on an ambulatory device used in a patient’s home environment.

The modeling algorithm developed in this thesis is subject-specific and is able to adapt to a patient’s changing daily life conditions, and also does not require any prior model tuning or training data. These features are achieved with the use of a patient’s own CGM data for model development and the online identification of the model parameters at each sampling step.

Patients with diabetes are also subjected to external disturbances such as meal consumption or physical activity that cause large blood glucose perturbations on a daily basis. A reliable model for predicting future glucose concentrations should also perform efficiently under such conditions without requiring any priori disturbance announcements or information. The modeling algorithm developed in this thesis is integrated with a change detection strategy for a faster adaptability and response in the presence of glycemic disturbances, and does not require any disturbance announcements.

Time-series analysis techniques are utilized in this thesis to develop subject-specific glucose prediction models using a subject’s CGM data. The model is recursively updated at each sampling time to dynamically capture any variation in the subject’s glucose metabolism. The recursive modeling strategy is also integrated with a change detection method to ensure faster response and convergence of model
parameters in presence of glycemic disturbances.

The proposed subject-specific models can simplify current diabetes management. For instance, predicted glucose concentrations can be used to provide early hypoglycemia or hyperglycemia alarms that allow patients to take corrective actions. Predicted glucose values can also guide patients with their daily insulin dose decisions and adjustments. Additionally, the models developed can be integrated with a model-based control algorithm to build a fully automated artificial pancreas.

The long-term complications of diabetes can be reduced by controlling a patient’s blood glucose concentration within the normoglycemic limits (i.e., 70-120 mg/dl). In the second phase of this research, the subject-specific modeling algorithm developed in Phase I is integrated with a model-based control algorithm for closing the glucose regulation loop for patients with type 1 diabetes. The objective is to keep blood glucose concentrations within tight control with postprandial levels below 160 mg/dl and normalization of glucose levels back to fasting range within 2-3.5 h after a meal challenge.

An adaptive control algorithm is developed to keep a patient’s glucose concentrations within normoglycemic range and dynamically respond to glycemic challenges with automated subcutaneous insulin infusion. A model-based control strategy is used to calculate the required insulin infusion rate, while the model parameters are recursively tuned. The closed-loop algorithm handles delays associated with insulin absorption, the time-delay between blood and subcutaneous glucose concentrations, and inter/intra-subject variations in glucose-insulin dynamics. The closed-loop system developed functions in a fully automated manner and does not require any disturbance announcements (e.g., meal time or amount) or patient intervention, and patient specific tailoring before implementation.
Closing the glucose control loop with a fully automated device will revolutionize management with diabetes and significantly improve the quality of life for patients with diabetes. As shown in Figure 2.1, such an automated artificial pancreas will consist of a glucose measuring device, an automated insulin infusion pump, and a control algorithm which computes the required insulin amount for the patient.

![Figure 2.1. Block diagram of an artificial pancreas.](image)

In this thesis, the availability of a reliable continuous glucose sensor and an insulin pump is assumed, and the focus is on development of a control algorithm that connects these two devices and provides fully automated blood glucose regulation. Subcutaneous route for both insulin delivery and glucose monitoring is considered. This is the most challenging route, since it contains large delays due to the slow insulin absorption (i.e., delay in input action), and a time-lag between subcutaneous (i.e., measured variable) and blood (i.e., controlled variable) glucose concentrations. Two well-known model-based control methods, the generalized predictive control (GPC) and the linear quadratic control (LQC), are used for control law computations, and their formulations are extended to include two time-delay compensators and a time-varying glucose reference trajectory.

Large delays associated with insulin absorption, time-lag between blood and subcutaneous glucose concentrations, wide range of inter-subject variability in glucose homeostasis and large glycemic disturbances such as meal consumption, exercise or stress are the major challenges for the blood glucose control problem. The control algorithm developed in this thesis is able to respond and provide effective control in
presence of all these challenges and does not require any disturbance announcements. Even though the control algorithm is developed and evaluated for the subcutaneous route for both glucose sensing and insulin delivery, its formulation allows the algorithm’s application for other routes as well, since the delay terms are explicitly expressed in the controller formulation.

Physical activity and emotional stimuli such as stress are known to have a significant effect on a subject’s whole-body fuel metabolism. In Phase III, the univariate glucose prediction models developed in Phase I are extended to include additional information on a patient’s physical and emotional condition. Real-time physiological measurements from a multi-sensor body monitor (e.g., armband) are used to supplement a patient’s CGM data and develop multivariate time-series models for predicting the patient’s future glucose excursions. The multivariate modeling algorithm developed improves the performance and the glucose prediction accuracy compared to the predictions done solely on CGM data (i.e., univariate modeling algorithm). Physiological measurements are wirelessly transmitted from an armband; thus, the effect of physical activity is captured without requiring any patient intervention.

Closing the blood glucose regulation loop with a fully automated system that also takes into account the effect of a patient’s physical and emotional condition on insulin requirements will significantly improve the lives of the patients with diabetes. Currently, patients have to manually adjust their insulin intake for anticipated physical activities. In the last part of this thesis, the closed-loop blood glucose control algorithm developed in Phase II is extended to utilize the multivariate modeling algorithm that uses not only a patient’s glucose measurements from a CGM device, but also several physiological signals depicting the patient’s physical activity and emotional conditions.

Similar to their univariate counterparts developed in Phase I and Phase II,
the multivariate modeling algorithm and the multivariate closed-loop algorithm developed in Phase III are subject-specific and dynamically capture inter-/intra-subject variability. They also do not require any prior experimental data, prior tuning for each subject, or disturbance announcements. Therefore, they can easily be implemented for any subject using a CGM sensor and a multi-sensor body monitor.
CHAPTER 3
LITERATURE REVIEW

3.1 Review of Existing Approaches to Modeling Glucose-Insulin Dynamics

Modeling glucose-insulin interaction in the human body has been an active research area for decades. In this section, a brief review of numerous models proposed in the literature is provided, by classifying them into two groups: (i) physiological models, and (ii) empirical models.

Most physiological models mathematically consist of ordinary differential equations. They aim to describe the physiology behind the regulatory mechanism of glucose or other metabolites. Physiological models are also known as compartmental models, since the body is divided into several compartments to represent the distribution of glucose and/or insulin in primary organs or tissues. Moreover, the compartment (organ) itself can be divided into two or more regions if there are mass transfer limitations within the compartment. Material balance equations are written around each compartment, resulting in a set of differential equations which are solved simultaneously. These models also include pharmacokinetic diagrams of exogenously administered insulin and glucose absorption from the gastrointestinal track following a meal consumption. Since blood glucose regulation is a highly nonlinear and complex process, most of the physiological models are generally representative of only an average subject under specific and disturbance free conditions, and they are typically nonlinear with too many parameters to be identified for individualized needs.

In contrast to physiological models, empirical models are based only on input-output data, and do not provide any insight about glucose-insulin dynamics. Empirical models are also known as black-box models (or data-driven nonparametric models), and are easy to develop and identify. Such models cannot be used to explain
the mechanism of a system, however, they can provide good predictions about its future behavior.

The glucose prediction modeling algorithm developed in this research falls into the empirical category, and since it is based on patient’s CGM data, the existing models in the literature that utilize CGM data are discussed separately in Section 3.1.3. Glucose-insulin models that consider the effect of exercise on glucose metabolisms are also discussed in a separate section (Section 3.1.4). One of the objectives of this research is to include the effect of activity into the modeling strategy by using physiological measurements from an multi-sensor body monitor that will supplement the CGM data.

3.1.1 Physiological Glucose-Insulin Models. The most extensively studied physiological model in the literature that describes glucose-insulin interactions in the human body [23] is the so-called Minimal Model (MM) [23], [24]. The model was originally proposed to interpret plasma glucose and insulin concentrations following an intravenous glucose tolerance test (IVGTT) in healthy subjects. In IVGTT test, subjects are injected with an intravenously administered glucose load, and the plasma glucose and insulin concentrations are measured at a high sampling rate. In the MM model, glucose-insulin interactions in the body are described with a two compartmental model that consists of three ordinary differential equations and few parameters. Plasma glucose dynamics, plasma insulin dynamics and insulin concentration in a remote inaccessible compartment are included in the model. Subject’s insulin sensitivity (how good the body responds to insulin) and glucose effectiveness (ability of glucose to stimulate its own uptake and suppress its own release) are established by this MM. However, the accuracy of the MM has been questioned by many researchers [25], [26], [27] and [28]. For instance, in [26], overestimation of the effect of glucose on glucose uptake and underestimation of the contribution of incremental in-
sulin by the MM are reported. Also, stability problems of the MM have been revealed by [28]. In [28], the authors show that the MM does not admit equilibrium and the insulin concentration in the remote compartment increases without bounds for some situations. However, the MM still remains as the most popular physiological model, because of its simple structure and minimum number of parameters which are easily identifiable.

The original MM model of [24] has been extended to include three subsystems (glucose, insulin and glucagon) in [29] and [30]. The effect of glucagon on glucose metabolism is explicitly included in this extended model. Glucagon is a counter-regulatory hormone that stimulates endogenous glucose production. In the extended MM model, the glucose and glucagon subsystems are each depicted with a single compartment, while the insulin subsystem consists of five compartments (plasma, liver, interstitial insulin, stored and promptly releasable pancreatic insulin). The glucose subsystem considers glucose production and uptake by liver, renal excretion, insulin-dependent and insulin-independent glucose utilization.

In a more recent study, the MM has been modified to provide the metabolic portrait of a whole population [31]. Originally, the MM has been proposed to demonstrate glucose metabolism of a single person. In [31], the authors propose a Bayesian approach for the population-based minimal model. Distributions of population insulin sensitivity and glucose effectiveness are computed using IVGTT data from 16 healthy people. Then, the mean and standard deviations of these population distributions are used as a priori information for individual analysis.

Another limitation with the MM is that it does not consider the absorption of exogenously administered insulin and the carbohydrate absorption from the gut after a food consumption. Lehmann and Deutsch [32] have improved the MM by adding intestinal glucose absorption to the model. This model attempts to reflect the
underlying pathophysiology of insulin action and carbohydrate absorption in quantitative terms such as insulin sensitivity, volume of glucose and insulin distribution, and maximal rate of gastric emptying in patients with type 1 diabetes. Similar to the original MM, a single glucose compartment is utilized. However, glucose enters into the compartment by intestinal absorption and hepatic production, and is removed by insulin independent glucose utilization in the red-blood cells, insulin dependent utilization in the liver and periphery, and renal glucose excretion.

Recent studies by Hovorka et al. [33] and [6] have extended the MM by adding an additional subsystem for insulin action. This subsystem considers the effect of insulin on glucose distribution/transport, glucose disposal, and endogenous glucose production. The glucose subsystem includes the renal glucose excretion, the endogenous glucose production, the insulin independent glucose flux, and the intestinal absorption. Finally, the insulin subsystem describes the subcutaneous insulin absorption and is partitioned into two compartments. The model parameters are identified employing a dual-tracer dilution methodology during an IVGTT.

A more extensive physiological model has been developed by Sorensen [34]. The body is divided into 7 compartments representing various body organs important for glucose regulation: brain, heart/lungs, gut, liver, kidney, and periphery. The model also includes glucagon dynamics and its interactions with the glucose-insulin system, and consists of total of 19 ordinary differential equations. The original model is proposed to represent glucose dynamics of a healthy person. However, by removing the equations that describe insulin release, the model is applied to patients with type 1 diabetes.

A similar physiological model has been proposed by Puckett [35] to describe glucose-insulin dynamics in a typical subject with type 1 diabetes. Except the interstitial insulin transport submodel, the model is developed from real patient data.
The data used for model development is obtained from subjects with type 1 diabetes taking both short- and long-acting insulin. The absorption rate of long-acting insulin is approximated as a zero-order process with constant rate. On the other hand the absorption of regular insulin from the subcutaneous tissue is represented with a two compartmental model. Insulin independent glucose uptake (glucose uptake by nervous system) rate is assumed constant. Glucose dependent glucose utilization is assumed to occur only in kidneys where glucose is excreted if the blood glucose concentration exceeds a limit of 176 mg/dl.

3.1.2 Empirical Glucose-Insulin Models. Many researchers believe that data-driven modeling approaches that do not require any prior assumptions about the model structure can provide accurate patient-specific models in a clinical context. The studies on these approaches range from Volterra-type models, artificial neural networks, probabilistic models, fuzzy models, to time-series analysis.

Tresp et al. [36] have developed neural network (NN) models for blood glucose metabolism. They compare the recurrent NNs and time-series convolution NNs with compartmental models. The data used consist of time and dose of insulin injections, amount of food intake, time and duration of exercise and SMBG measurements of a male patient with type 1 diabetes over a period of 63 days. A linear error model is also included to take into account the uncertainty in the system and for handling missing data points. The recurrent NN combined with the error model is reported to provide superior results compared to a compartmental model or the time-series convolution NN method.

Another neural network approach has been proposed by [37] to recommend appropriate insulin type and dose adjustments for a short-period of time. The system consists of two feed-forward NNs. The first NN recommends the appropriate insulin regimen, while the second one estimates the insulin dose required. Six different in-
sulin regimens of various combinations of regular and intermediate-acting insulin are considered by this decision support system. The performance of the proposed method is shown to be highly dependent on data used for training.

Same authors have also proposed a hybrid system composed of compartmental models (CMs) and artificial NNs for simulation of glucose-insulin metabolism [38]. The data used consist of SMBG measurements, insulin and food intake information. The data is fed to three separate CMs to estimate (i) resulted plasma insulin concentration due to regular insulin injection and (ii) intermediate-acting insulin injection, and (iii) glucose absorption from the gut after a meal consumption. The outputs of the CMs are then fed to a recurrent NN trained with real time recurrent learning algorithm to provide short-time predictions of blood-glucose levels. Promising results are reported in terms of prediction accuracy.

Empirical Volterra series models of glucose-insulin dynamics have been developed by [39]. In absence of noise, the nonlinear Volterra models are shown to provide accurate glucose predictions. However, significantly degraded estimates are reported in presence of noise. The models developed are also integrated with a linear and a nonlinear model predictive control (MPC) algorithm and are evaluated for rejecting a 50 $g$ glucose challenge. The linear MPC with ability to filter the effect of noise by proper tuning is reported to provide the best closed-loop performance.

In a similar study, Mitsis and Marmelis [40] have developed Volterra-type models from input-output data generated by a simulation study. Minimal model is used for data generation, and assumed to represent the actual closed-loop operating conditions of the system. Laguerre-Volterra Network (LVN) methods which provide accurate representation of high-order systems from short input-output data are employed. Iterative gradient descent scheme is utilized for LVN training. Results demonstrate the feasibility of obtaining data-driven nonparametric models. The au-
The authors also demonstrate that data-driven models are more responsive to adaptive and patient-specific estimation compared to physiological models.

In another study, a compartmental model of glucose metabolism has been implemented as a causal probabilistic network (CPN) [41]. The CPN model is a discrete-time model with one-hour sampling step, and includes three state variables (current plasma insulin, blood glucose, and amount of carbohydrate consumed). Predictions of 24 h blood glucose profiles are generated as probabilistic distributions over a range of blood glucose concentrations. Additionally, these predictions are used to develop a decision support system for insulin dose adjustments. A penalty is assigned to each level of glucose, and a risk factor is calculated to describe the probability of weighted average of the penalties. Insulin dose that provides the minimum risk is advised for the patient.

A hybrid method that integrates qualitative modeling techniques with fuzzy logic systems has been developed by [42] for predicting blood glucose levels. The fuzzy inference procedure is initialized with a priori structural knowledge on the system, and functional approximation of the system dynamics is determined using experimental data.

A mixed graphical model technique has been utilized by [43] to develop a glucose-insulin model described by stochastic linear differential equations. Model parameters and error parameters are represented as uncertain parameters with a-posteriori distributions (interpreted as fuzzy possibility distributions), and are identified by means of an exact inference algorithm.

Yamaguchi et al. [44] have used a data mining strategy for predicting fasting blood glucose (FBG) levels as a function of metabolic rate, food intake, and physical condition. FBG levels have also been estimated using chaos theory, [45] and [46].
Bayesian analysis as an off-line tool, [47] and [48], has been proposed to evaluate the structural trends and daily cycles of self-monitored glucose data.

### 3.1.3 Empirical Models from Continuous Glucose Monitoring Data.
Recent technological advances in the glucose monitoring provide more insight into patient’s glucose profile throughout the day. Frequently measured glucose data enable obtaining more reliable data-driven (empirical) models of glucose-insulin interaction.

A Kalman filter (KF) has been developed in [49] to estimate blood glucose concentrations from noisy subcutaneous glucose sensor signals. On a simulation study, KF is used to estimate one-step-ahead blood glucose concentrations and rate-of-change of blood glucose from subcutaneous glucose measurements (noise with standard deviation of 1 mg/dl added to the simulated signal). The estimated rate-of-change of blood glucose is then used to predict glucose concentrations $n$-steps into the future. The authors discuss that predicted glucose concentrations can be used to provide early alarms for patients to take corrective action and avoid hypoglycemia.

Another study by the same group, implements a KF to estimate the first and second rate-of-change of subcutaneous glucose measurements [50]. These estimates are then used to predict future glucose concentrations. A simulated sinusoidal signal is used to represent the subcutaneous glucose profile. Sensitivity and specificity of predicting hypoglycemia is demonstrated for sampling intervals of 1 min to 30 min with prediction horizons up to 30 min, and threshold for hypoglycemia from 40 mg/dl to 100 mg/dl. For 1 min sampling interval, authors report good prediction performance even with long prediction horizons. However, increasing the sampling period is shown to result in steady deterioration.

Knobbe and Buckingham [51] have also used the KF theory. They have developed a five-state extended KF to estimate subcutaneous and blood glucose levels,
time lag between the sensor measured subcutaneous glucose and the blood glucose, rate-of-change of blood glucose levels, and subcutaneous glucose sensor scale factor. Results are demonstrated on data collected from four patients with diabetes.

A time-series approach has been implemented by [52] for analyzing continuous glucose monitoring data. Autoregressive exogenous input (ARX) and Box-Jenkins (BJ) models with constant parameters and various model orders (high and low) are identified using simulated input-output data. Prediction of future glucose concentrations (model output) are based on insulin infusion rate, intestinal glucose absorption rate and previous model outputs. Models identified from non-faulty data are also applied to four faulty data sets (50% reduction in insulin sensitivity, pump occlusion, 50% underestimated carbohydrate amount of meal and 15 min mismatch between actual and patient-reported meal time) to test the ability of a fault detection. High- and low-order models are shown to provide comparable results under normal operating conditions. However, low-order models failed to distinguish between normal and faulty operation.

A time-series model has also been implemented by [53] for predicting glucose concentrations of critically ill patients in the intensive care unit. Data from 41 patients are analyzed for the identification of a time-invariant (constant parameters) ARX model. The model inputs consist of 12 variables (arterial glucose concentration, insulin infusion rate, insulin resistance, total carbohydrate calories, total fat calories, body temperature, glucocorticoids, adrenalin, noradrenalin, dobutamin, dopamine, and beta-blockers), each measured at one or 4 h interval. From these inputs two-previous glucose measurements, insulin infusion rate, insulin resistance, total carbohydrate calories and dopamine are found to significantly affect the glucose levels.

Sparacino et al. [54] have investigated the possibility to predict future glucose concentrations using patient’s recent CGM history. Differently from [52] and [53],
the only input to the time-series models is the past glucose measurements. Continuous glucose monitoring data with sampling period of 3 min of 28 real patients with type 1 diabetes are utilized in this study. A first-order polynomial and a first-order autoregressive (AR) model are developed for each patient. The models are recursively identified at each sampling step using weighted linear least squares method. Results demonstrate that glucose prediction using past measurements is feasible, and that the performance of the proposed algorithms is adequate for preventing hypo/hyperglycemic events with early alarms. The authors suggest that investigating data provided by other CGM sensors and more sophisticated autoregressive models is worthwhile.

3.1.4 Models for Glucose-Insulin Dynamics during Exercise. Exercise is known to increase glucose utilization and production by a factor of 3 to 4 without perturbing the arterial glucose concentration in healthy people. Even though exercise has a significant effect on the whole-body fuel metabolism, only a few studies are available in literature that model glucose and insulin homeostasis during exercise.

Kim et al. [55] has developed an extensive physiological model of the whole-body metabolism during moderate intensity exercise. The model consists of seven tissue compartments (brain, heart, liver, gastrointestinal tract, skeletal muscle, adipose tissue, and other tissues). Each tissue compartment is represented with dynamic mass balances and cellular metabolic reactions. The effect of moderate exercise is captured with increased ATP utilization in the heart and the skeletal muscle. A glucagon-insulin controller is incorporated into the whole body model to predict hormonal changes during exercise. Arterial epinephrine level is provided as an input function, which directly affects heart and skeletal muscle metabolism and indirectly other tissues via the glucagon-insulin controller. The model differentiates tissues with distinct metabolic pathways. It also includes transport and biochemical reactions of major
fuel sources, and incorporates the effect of hormonal control by insulin, glucagon, and epinephrine to regulate the metabolic processes in each tissue, and consequently, the effect of related cellular metabolic processes and their regulation to whole body responses.

Roy [56] has extended the 2-compartmental MM to incorporate the effects of exercise on glucose and insulin dynamics. Physical activity is expressed as a percentage of maximum capacity of an individual for aerobic work (maximal oxygen consumption). MM is modified to include the rate of insulin removal from the circulatory system due to exercise-induced physiological changes, and the rates of glucose uptake and hepatic glucose production induced by exercise. A term representing the decline of glycogenolysis rate during prolonged exercise due to depletion of liver glycogen stores is also added to MM formulation. The developed model aims to capture the changes in glucose and insulin dynamics during and after mild to moderate intensity exercise.

Rollins et al. [57] has emphasized the significance of physiological signals on glucose profiles after analyzing the data from an armband that provides continuous metabolic physical activity information. The device consists of several sensors for measurement of heat-flux (heat dissipated by the body), skin-temperature, near body temperature, galvanic skin response (which varies due to sweating and emotional stimuli), and a two-axis accelerometer (tracks movement and body position). The signals from the armband with additional detailed information of subject’s food intake are used to develop an empirical model for prediction of subject’s future glucose concentrations. A block-oriented Wiener modeling approach that consists of several linear blocks (as many as number of inputs) and a nonlinear static block is utilized for this purpose. The models are validated using real patient data. Identification of the model parameters of the nonlinear and linear blocks is performed by prior off-line
analysis of 20-days of training data. Prediction performance of the models developed are shown to be highly dependent on the relationship between testing and training data.

3.2 Review of Existing Approaches to Closed-Loop Blood Glucose Regulation

The following is a brief review of literature studies that have proposed different control algorithms for closing the glucose regulation loop with an automated artificial pancreas. Studies are presented in chronological order.

The work of Kadish [22] is recognized as the first attempt towards the artificial pancreas. In 1964, Kadish [22] has closed the glucose regulation loop with intravenous infusion of both insulin and glucagon using an ‘on-of’ control system. In 1974, Albisser et al. [58] and Pfeiffer et al. [59] have combined glucose measurements with algorithms implemented on a microcomputer to automate insulin and glucose (i.e., dextrose) infusions. In the study of Pfeiffer et al. [59], the insulin infusion rate is proportional to the change of blood glucose concentration, and dextrose is infused when needed (i.e., low blood glucose levels). On the other hand, in Albisser et al. [58], dextrose and insulin infusion rates are calculated based on the current blood glucose measurement, the rate of glucose change and the predicted blood glucose value. At each sampling step, predicted blood glucose concentration is calculated as a projection of the current measured glucose at a four-minute-average rate of change.

The first commercial device, Biostator [60] (Miles Laboratory Inc., Michawaka, IN, USA), required withdrawal of venous blood from the patient for measuring glucose concentrations ex vivo. Both glucose and insulin were infused intravenously based on a nonlinear proportional-plus-derivative control algorithm. This bulky device was suitable for bedside use only. This and couple of other early attempts of artificial pancreas are compared by Broekhuysse et al. [61] who conclude that no single controller
was uniformly superior and further work was required for satisfactory results.

After the bedside Biostator, weighting around 60 kg, the first attempt for a miniaturized, portable device (about 400 g in weight) came out by Shichiri et al. [62], [63]. Recently, the group of Shichiri [64], [65] have also proposed development of both a reliable subcutaneous glucose monitoring system and a subcutaneous insulin infusion algorithm. Glucose is monitored by a miniaturized extracorporeal system based on microdialysis sampling method or a ferrocene-mediated needle-type glucose sensor covered with poly(MPC-co-BMA) membrane. In healthy subjects, blood glucose and insulin concentrations are assumed to be described by the proportional derivative control law. And insulin infusion rate is calculated by the pole-placement strategy to depict healthy pancreatic function. The algorithm is tested on 10 patients with type 1 diabetes after a 75 g oral glucose load and during standard daily glucose control that includes 3 meal consumptions. Results show that with the proposed algorithm for subcutaneous infusion of rapid-acting insulin, near normal glycemic control is achieved.

Sorensen [34] has used the internal model control theory to develop a linear model based controller that regulates patient’s glucose levels. In [34], a comprehensive 19th-order nonlinear compartmental model describing the glucose-insulin dynamics in the human body is developed. This model is then approximated to a first-order-plus-time-delay transfer function and used in controller computations.

In their study, Fisher and Teo [66] use the optimal control theory to compute the insulin infusion rates. They minimize a quadratic cost function that consists of the sum of squared glucose tracking errors and a penalty term on the control action. Insulin delivered by a single injection, constant continuous infusion, and closed-loop infusion are compared for their performances to reduce the initially high glucose levels and control of blood glucose levels following a meal. The single injection is found to
be superior to other infusion protocols. Similar approach (optimal control theory) has been investigated by Swan [67] and Ollerton [68].

Brunetti et al. [69] has proposed a self-tuning, minimum variance implicit algorithm for intravenous insulin delivery. Recursive least-square method is used to develop a linear mathematical model from input-output data. Controller parameters are calculated to minimize a performance index. The proposed control algorithm is tested with simulation studies that utilize a nonlinear glucose-insulin dynamics model. Each simulation consists of an oral glucose tolerance test (OGTT) performed twice. The first OGTT is used for self-tuning of the controller, while the second OGTT is used for performance evaluation. Another adaptive control algorithm has been proposed by Candas and Rarziuk [70] during a glucose clamp study for adjusting the exogenous glucose infusion rates. A nonlinear model of glucose-insulin dynamics is utilized to estimate the time course of insulin dependent glucose removal rate. The exogenous glucose infusion rate required to keep the glucose concentration at a predefined level is computed based on the predicted insulin action. Simultaneously, the model parameters are recursively updated at each sampling time allowing the fine-tuning of the controller with the new data. The algorithm is tested to maintain glycemia in three pigs during intravenous or subcutaneous insulin injection and staircase infusions of insulin. In another study, Fischer et al. [71] have demonstrated that controller algorithms exhibit superior performance when the model parameters are updated online or made patient specific.

Due to the uncertainty in the glucose-insulin dynamics, Kienitz and Yoneyama [72] have used the H-infinity theory to control glucose levels. In their study, a feedback control algorithm that achieves desired blood glucose levels and simultaneously presents robustness to the uncertainties in the model parameters is developed. The designed controller is of full-state-feedback type and does not require a priori infor-
Trajanoski et al. [73] have proposed an approach called neural predictive control for artificial pancreas with the subcutaneous route. The proposed framework combines off-line identification of a nonlinear autoregressive model using a regularization approach for constructing radial basis function neural networks and a nonlinear MPC strategy using the previously identified model. The effects of various noise levels for the subcutaneous glucose measurement, additional time delay, and time variation of the glucoregulatory system are also investigated.

In [74], [75], and [76], Parker et al. have explored the use of model predictive control (MPC) for regulation of blood glucose. In [74], a linear MPC with state estimation that takes into account patient variability is shown to be superior to the standard input-output model based MPC (dynamic matrix control). The controller performance is evaluated for setpoint tracking (reducing the elevated glucose levels to a predefined value), and unmeasured disturbance rejection (meal consumption). In [75], formulations for linear MPC, MPC with state estimation, and nonlinear quadratic dynamic matrix control with state estimation are provided and applied to a simulated subject with type 1 diabetes subjected to a 50 g OGTT (unmeasured disturbance rejection). In [76], Parker et al. utilize standard MPC using an asymmetric objective function where the hypoglycemic values are much less tolerable than the hyperglycemic values. Lynch and Bequette [77] have also proposed estimation based MPC for blood glucose regulation in subjects with type 1 diabetes. Differently from the studies of Parker et al. [74], [75], [76], their approach is based on constrained MPC. Controller performance is evaluated on a simulated patient subjected to a 50 g meal disturbance.

Steil et al. [78], [79], [80] have discussed that the biphasic insulin response of beta-cells of pancreas can be most closely represented with a PID control algorithm,
thus there is no need for the complicated model based algorithms. The first phase of body’s insulin secretion is associated with the rate of change of blood glucose (derivative action), while the second phase is associated with the deviation of blood glucose from its basal value (integral action). The algorithm is first tested on dogs [78] and then on six patients with type 1 diabetes over a 27.5 h time period that includes four meal consumptions [79].

The results of a three-year European project of artificial pancreas are presented in [6], [81]. In order to take into account inter- and intra-patient variability, the nonlinear MPC approach is combined with Bayesian estimation of model parameters at each sampling time. The intravenously measured glucose data is delayed by 30 min to simulate the time delay associated with the subcutaneous glucose sampling. An asymmetric target glucose trajectory is utilized to ensure faster recovery from low glucose values (i.e., hypoglycemia). The algorithm is tested on 15 patients with type 1 diabetes over a 8-10 h time period to regulate glucose levels during fasting conditions.

Control algorithms developed for diabetic patients under intensive care include works of Chee et al. [82], [83] and Kovacs et al. [84]. Chee et al. explore the proportional-integral (PI) [82] and expert PID [83] control strategies based on a sliding scale approach. The sliding scale approach is usually utilized by clinicians to adjust the intravenous insulin infusion rate on a hourly basis. It divides the range of blood glucose concentration into regions and an insulin infusion rate is assigned for each region. In [82], the insulin dose is determined based on basic dose plus an offset term. The basic dose provides the proportional control action and is determined from the sliding scale table, while the offset corresponds to the integral action and is based on the direction of blood glucose change. In [83], Chee et al. have extended the PI algorithm to an expert PID controller. Derivative action is included to boost the
insulin infusion during a rapid increase of blood glucose, and an expert controller is triggered when the blood glucose concentrations cross predefined boundaries. On the other hand Kovacs et al. \cite{84} have utilized the linear quadratic (LQ) optimal control strategy, and its extension to disturbance rejection (LQR) based on MINIMAX criteria. For the latter case, the input variable is separated into two: the control input and the immeasurable disturbance. The main objective is to calculate the control input that minimizes the maximum cost achievable by the worst-case disturbance.

The recent work of \cite{85} has proposed a brain-inspired neural fuzzy system as a controller for closed-loop insulin delivery. Pseudo-outer product based fuzzy NN that employs a two-phase training algorithm is implemented using the Yager rule of interface. The principles of the proposed Yager system is inspired by the learning mechanisms of the biological brain. Results are demonstrated on simulated patient, and the testing and training data is obtained from healthy person models of GlucoSim \cite{86}.

Eren-Oruklu et al. \cite{87} have developed an implicit self-tuning tracker to keep glucose concentrations of patients with type 1 diabetes within normoglycemic range with subcutaneous insulin infusion. The controller parameters are tuned at each sampling step, and the changes in the glucose-insulin time series model are directly integrated to the control strategy.

El-Khatib et al. \cite{88} have developed a bihormonal (i.e., insulin and glucagon) closed-loop artificial pancreas for type 1 diabetes. The control algorithm proposed is initialized with subject’s weight and uses venous blood glucose data measured every 5 min. A generalized model predictive control (GPC) algorithm is used to compute the required insulin dose. The GPC incorporates a pharmacokinetic (PK) model of subcutaneous insulin absorption and insulin clearance from the blood to account for insulin-on-board. Additionally, a proportional-derivative (PD) control algorithm,
with an online accumulation term, is used to calculate the required glucagon amount for preventing or treating glucose levels below 100 \text{mg/dl}. Both glucagon and insulin are administered as subcutaneous boluses every 5 \text{min}. The proposed bihormonal algorithm is tested on 11 patients with type 1 diabetes over 27 \text{h} during which subjects consumed 3 carbohydrate-rich meals. Five of the subjects experienced hypoglycemia in the late postprandial period despite higher glucagon delivery. Post-analyses have shown that these subjects had a slower insulin absorption rate and in order to prevent hypoglycemia, off-line tuning of the insulin PK model is required for each individual patient.

Renard et al. [89] have utilized the proportional-integral-derivative (PID) control theory to close the glucose regulation loop via intraperitoneal insulin infusion from an implanted pump driven by a subcutaneous glucose sensor. Eight subjects with type 1 diabetes, treated by an implanted pump were hospitalized for a total of 86 \text{h}, which was divided into a preparation phase (14 \text{h}), and randomized open-loop (24 \text{h}) and closed-loop (48 \text{h}) phases. During the open-loop phase, patients took 7 fingerstick glucose measurements and accordingly adjusted their insulin pumps. During the closed-loop phase, discrete boluses of insulin were delivered automatically every 1 \text{min} and a manual pre-meal bolus (consisting of 30\% of the amount the patient would have programmed) was given 15 \text{min} before each meal. Controller parameters were individualized off-line for each subject as a function of their total daily insulin dose. Results show that mean percentage of time spent within normoglycemia are higher during the closed-loop phase compared to the open-loop phase.

In a multinational study, Kovatchev et al. [90] have tested a model predictive closed-loop algorithm on 20 patients with type 1 diabetes during overnight and breakfast for 14.5 \text{h}. Subject’s body weight, total daily insulin dose, carbohydrate to insulin ratio and basal insulin rate are used to tailor the MPC algorithm off-line for
each person. Additionally, meal time and amount are announced to the controller before closing the loop, which permits the MPC to anticipate the meal disturbances. When compared to a patient-directed open-loop control study, closed-loop control is shown to significantly reduce nocturnal hypoglycemia. However, the performance of the MPC algorithm before and after breakfast is found to be inferior to the open-loop control.

3.3 Shortcomings of Existing Modeling and Control Approaches

3.3.1 Shortcomings of the Existing Modeling Approaches. The physiological models proposed in the literature are generally representative of only an average subject under predefined and disturbance free conditions. These models are typically nonlinear with too many parameters to be identified. Therefore, most of them are not suitable for implementation in glucose prediction or model-based closed-loop control algorithms without significant additional modeling effort for individualized needs of each patient.

Data-driven empirical models cannot be used to explain the mechanism of glucose-insulin metabolism in detail, however, they can provide good predictions about future behavior of glucose observations. Proposed data-driven models that utilize Volterra-type model [40], [39], artificial neural networks [36], [37], [38], probabilistic [41] and fuzzy model [42], [43] approaches require prior experimental data for model development. Therefore, their efficiency is highly dependent on data used for training.

Furthermore, most of the proposed empirical models necessitate inputs such as food intake or physical condition information ([36], [38], [44], [45], [46], [47], [48], [53]). Such models are not suitable for a fully automated closed-loop system, since they will require frequent patient input (e.g., meal size).
Among the empirical models developed from CGM data, [50] use an unrealistic simulated sinusoidal signal to represent a typical glucose concentration profile of a patient with diabetes.

Studies of [52], [53] and [54] support the use of time-series analysis for prediction of glucose concentration profiles. The model developed by [52] is validated on simulation data only, and requires both glucose and insulin infusion rate observations. Similarly, [53] requires additional inputs such as two-previous glucose measurements, insulin infusion rate, insulin resistance, total carbohydrate calories and dopamine. Differently, in the first part of this thesis, univariate time-series models that use only recent glucose measurements are developed. The model predicts future glucose concentrations based on two-previous glucose measurements (similar to [53]) and a residual term. The model of Sparacino et al. [54] also utilizes glucose data only. However, the univariate models developed in this thesis are based on a different model type and order, and a recursive identification technique that integrates a change detection strategy to identify the model parameters is employed.

In the third part of this thesis, empirical multivariate models that utilize patient’s CGM data and physiological measurements from an armband through wireless communication are also developed. Thus, the effect of physical activity is included without requiring any patient intervention. Similarly, Rollins et al. [57] propose empirical models that utilize data from an armband. However, the models are not recursive and their prediction performance is shown to be highly dependent on training data. Works of [55] and [56] extend the regular glucose-insulin physiological models to include the effect of exercise. However, these models still possess the drawbacks of physiological models.

3.3.2 Shortcomings of the Existing Control Approaches. In healthy subjects, blood glucose concentrations are regulated within tight limits. This range is 70-90
mg/dl of glucose during fasting conditions. Following a meal, glucose concentrations increase to 120-160 mg/dl depending on the meal size. A closed-loop algorithm for blood glucose regulation should mimic these healthy subject conditions.

Early closed-loop attempts include intravenous infusion of both insulin and glucose [58], [59], [60] (or glucagon [22]). Regulating glucose levels with infusion of both insulin and glucose/glucagon is much easier compared to insulin only infusion, since the hypoglycemic episodes can easily be recovered with glucose/glucagon infusion.

Most of the control algorithms proposed for blood glucose regulation consider the intravenous insulin administration [22], [34], [69], [74], [75], [76], [77], [82], [83] [84]. Intravenous route is associated with minimum delay in insulin action, and consequently rejection of large disturbances like meal ingestion is easier compared to subcutaneous route. However, subcutaneous route is less invasive and currently most of the commercial insulin pumps prefer this route.

Most of the studies proposing model-based control strategies [74], [75], [76], [77] are validated on simulation data for rejecting a single meal consumption or OGTT. However, more realistic daily life glycemic disturbances include several meal consumptions. Consecutive meal consumptions may occur before the normalization of glucose levels following the first meal. For such situations, the increased insulin infusion rate during the first meal will still be present in the bloodstream, and have effect on insulin requirements for the second meal. Additionally, strategies of [74], [75], [76], [77] utilized physiological glucose-insulin models that are typically nonlinear with too many parameters to be identified for individualized needs.

There have been clinical studies testing classical feedback control (PID [78], [79], [80] or PD [64], [65]) with subcutaneous insulin administration. However, they
all reported significantly higher postprandial glucose levels than those observed in healthy subjects under similar conditions. In [89], a PID algorithm with a manual pre-meal bolus has been tested for intraperitoneal insulin infusion via an implanted pump. The intraperitoneal route which is associated with no-delay in insulin action and the manual pre-meal bolus makes the glucose control problem much easier.

Clinical studies that used a model-based control strategy and the subcutaneous glucose-insulin route have been conducted by [6] and [90]. However, in [6], the MPC algorithm is not tested for rejecting a meal challenge; instead, it is only tested for maintaining fasting glucose levels. And in [90], meal time and amount are announced to the controller in advance, and still the closed-loop results are reported to be inferior to a open-loop control study after a meal consumption. Similarly, El-Khatib et al. [88] developed a model-based controller and tested it on patients with type 1 diabetes for meal rejection without prior meal announcement. However, they measure patient’s venous blood glucose (instead of subcutaneous) and simultaneously deliver glucagon to prevent or treat hypoglycemia which make the blood glucose control problem easier.
CHAPTER 4
MODELING ALGORITHM FOR ESTIMATION OF FUTURE GLUCOSE CONCENTRATIONS

The individual components of the modeling algorithm developed for predicting future glucose concentrations is introduced in this chapter. Time-series methods are utilized to analyze a patient’s continuous glucose monitoring (CGM) data and physiological measurements from a multi-sensor body monitor. Patient’s data are used to develop univariate and multivariate empirical subject-specific linear models. Model parameters are recursively identified at each sampling step to include the information from the new measurements. A change detection method which aims to identify glucose fluctuations due to possible disturbances is also incorporated to the modeling algorithm.

In this chapter, first, the challenges and the necessary features of a glucose predicting strategy are discussed. Next, the mathematical components of the modeling algorithm developed are individually described.

4.1 Challenges

Glucose-insulin dynamics show great variability from subject to subject. Metabolic changes that are caused by stress, illness or changes in insulin sensitivity may also lead to variation in glucose-insulin dynamics within the same subject. Furthermore, patients with diabetes are subjected to external disturbances such as meal consumption and physical activity that cause large blood glucose perturbations on a daily basis. A reliable model for predicting future glucose concentrations should address such variabilities and should be able to adapt to unexpected glycemic perturbations. In other words, reliable models are required to be subject-specific. For many modeling strategies, this will require prior experimental data from each patient for off-line tuning of the model parameters, and therefore, may limit the strategy from
being implemented on an ambulatory device used in a patient’s home environment.

Another important aspect is the adaptability of the model. A reliable model should be able to capture any variation in a subject’s glucose metabolism with changing daily life conditions. This can be achieved with online identification of the model parameters.

Both the univariate and the multivariate modeling algorithms developed in this thesis are subject-specific and are able to adapt to a patient’s changing daily life conditions and also do not require any prior model tuning or training data. These features are achieved with the use of a patient’s own CGM and arm band data for model development and the online identification of the model parameters at each sampling step. For a faster adaptability and response in the presence of glycemic disturbances, the algorithms are also incorporated with a change detection strategy.

4.2 Time-Series Models

Time-series methods are used for analysis of an ordered sequence of observations that are sampled at intervals equally spaced in time. Many sets of data fall into time-series type, such as the yields of consecutive batches from a chemical process, the price of an asset in stock market, the monthly unemployment rates, or the mean monthly temperatures of a city. Therefore, the time-series analysis is a widely used method in various fields (e.g., engineering, economics, business, meteorology and other natural sciences).

The intrinsic feature that differentiates time series data from other types of data is that, the observations at consecutive time instants will be related and dependent. Time-series analysis takes into account that the data taken over time may have an internal structure, and aims to uncover the underlying relationship in the data responsible for the observed behavior. An important characteristic of time-series models
is that the behavioral pattern is described simply by examining the past sequence of observations. Once the behavioral pattern of the observed data is identified, it can be used for predicting the future values of the observed variables. Time-series models can also be used for determination of the transfer function (i.e., a dynamic input-output model) of a process that describes the effect of given time-series inputs on the system output(s) in discrete time-domain, or for the design of control algorithms which aim to minimize the deviations of the system output from a desired trajectory by adjusting the values of the input time-series.

4.2.1 Univariate Time-Series Models. Time-series models have many forms. Still, they can be classified into two main classes: (i) autoregressive (AR), and (ii) moving average (MA) models. All other forms of time-series models are various combinations or modifications of AR and MA models.

The AR model expresses the observation at the time instant \( k \) as a finite, weighted sum of \( n_A \) previous observations, plus a noise term:

\[
y_k = \sum_{i=1}^{n_A} a_i y_{k-i} + \epsilon_k \tag{4.1}
\]

where \( y_k \) is the observation (i.e., system output) at the \( k \)th sampling instant. \( a_i \)'s are unknown model parameters, and \( n_A \) defines the model order, AR(\( n_A \)). \( \epsilon_k \) represents white noise. In (4.1), \( y_k \) is regressed on its own past values, hence the model is named autoregressive.

Differently, for some cases it can be more practical to assume \( y_k \) as a linear combination of a sequence of uncorrelated random variables \( \{\epsilon_k\} \):

\[
y_k = \sum_{i=1}^{n_C} c_i \epsilon_{k-i} + \epsilon_k \tag{4.2}
\]
(4.2) is referred as MA model. Model order is defined by \( n_C \), MA(\( n_C \)), and \( c_i \)'s correspond to model parameters.

The drawback with either AR or MA models is that a high-order model might be required to achieve a good fitting for some data sets. In general, large number of model parameters reduces the efficiency in parameter estimation or model identification. Therefore, to achieve greater flexibility in fitting with lesser number of parameters, combination of the AR and MA modeling features can sometimes be more advantageous:

\[
y_k = \sum_{i=1}^{n_A} a_i y_{k-i} + \sum_{i=1}^{n_C} c_i \epsilon_{k-1} + \epsilon_k
\]

Equation (4.3) is known as autoregressive moving average ARMA(\( n_A, n_C \)) model. ARMA model structure can lead to much simpler models with greater explanatory power compared to AR or MA models.

In a more general form, ARMA(\( n_A, n_C \)) can be expressed as:

\[
A(q^{-1}) y_k = C(q^{-1}) \epsilon_k
\]

where the polynomials \( A(q^{-1}) \) and \( C(q^{-1}) \) are represented by:

\[
A(q^{-1}) = 1 - a_1 q^{-1} - \ldots - a_{n_A} q^{-n_A}
\]

\[
C(q^{-1}) = 1 + c_1 q^{-1} + \ldots + c_{n_C} q^{-n_C}
\]

and the back-shift operator \( (q^{-1}) \) is defined by \( y_k q^{-i} = y_{k-i} \).

The time-series data can also contain observations of both input and output variables. In this case, autoregressive moving-average model with exogenous inputs ARMAX(\( n_A, n_B, n_C \)) model structure is more relevant:
\[ A(q^{-1}) y_k = q^{-d} B(q^{-1}) u_{k-1} + C(q^{-1}) \epsilon_k \] (4.7)

This model structure also includes the effect of past input variables, \( \{u_{k-i}\} \), on the system output \( y_k \). In (4.7), \( u_k \) represents the process input variable at the \( k \)th sampling instant. \( d \) is the delay term and \( q^{-d} \) describes \( d \)-steps of delay for the input action. Polynomial \( B(q^{-1}) \) has similar definition to (4.5) and (4.6):

\[ B(q^{-1}) = b_0 + b_1 q^{-1} + \ldots + b_{n_B} q^{-n_B} \] (4.8)

where \( n_B \) is the polynomial order of \( B(q^{-1}) \) and \( b_i \)’s are the additional model parameters.

In terms of ARMA model defined in (4.4), the process is non-stationary if some roots of its AR polynomial do not lie outside the unit circle. In such a case, a stationary process might be achievable by:

\[ A(q^{-1}) y_k = \tilde{A}(q^{-1}) \nabla^p y_k = C(q^{-1}) \epsilon_k \] (4.9)

where the polynomial \( \tilde{A}(q^{-1}) \) has all its roots outside the unit circle, and \( \nabla^p \) contains the roots of \( A(q^{-1}) \) that are inside the unit circle. \( \nabla^p \) is known as differencing operator and is defined by \( \nabla^p = (1 - q^{-1})^p \). Equation (4.9) is known as autoregressive integrated moving-average (ARIMA) model. Similarly, a non-stationary ARMAX model defined in (4.7) can take the following stationary form:

\[ \tilde{A}(q^{-1}) \nabla^p y_k = q^{-d} \tilde{B}(q^{-1}) \nabla^p u_{k-1} + C(q^{-1}) \epsilon_k \] (4.10)

which is known as autoregressive integrated moving-average model with exogenous inputs (ARIMAX) model.
4.2.2 Multivariate Time-Series Models. Multivariate processes arise when several related variables are observed simultaneously over time. Suppose that \( m \) related time-series variables are considered, \( y_{1,k}, y_{2,k}, \ldots, y_{m,k} \). The univariate ARMA model is extended to multivariate model called vector ARMA (or VARMA) that is described by:

\[
\begin{bmatrix}
  y_{1,k} \\
y_{2,k} \\
  \vdots \\
y_{m,k}
\end{bmatrix}
= \begin{bmatrix}
  a_{11,1} & \cdots & a_{1m,1} \\
a_{21,1} & \cdots & a_{2m,1} \\
  \vdots & \ddots & \vdots \\
a_{m1,1} & \cdots & a_{mm,1}
\end{bmatrix}
\begin{bmatrix}
  y_{1,k-1} \\
y_{2,k-1} \\
  \vdots \\
y_{m,k-1}
\end{bmatrix}
+ \ldots
\]

\[
+ \begin{bmatrix}
  a_{11,n_A} & \cdots & a_{1m,n_A} \\
a_{21,n_A} & \cdots & a_{2m,n_A} \\
  \vdots & \ddots & \vdots \\
a_{m1,n_A} & \cdots & a_{mm,n_A}
\end{bmatrix}
\begin{bmatrix}
  y_{1,k-n_A} \\
y_{2,k-n_A} \\
  \vdots \\
y_{m,k-n_A}
\end{bmatrix}
+ \begin{bmatrix}
  \epsilon_{1,k} \\
  \epsilon_{2,k} \\
  \vdots \\
  \epsilon_{m,k}
\end{bmatrix}
\]

\[
+ \begin{bmatrix}
  c_{11,1} & \cdots & c_{1m,1} \\
c_{21,1} & \cdots & c_{2m,1} \\
  \vdots & \ddots & \vdots \\
c_{m1,1} & \cdots & c_{mm,1}
\end{bmatrix}
\begin{bmatrix}
  \epsilon_{1,k-1} \\
  \epsilon_{2,k-1} \\
  \vdots \\
  \epsilon_{m,k-1}
\end{bmatrix}
+ \ldots + \begin{bmatrix}
  c_{11,n_C} & \cdots & c_{1m,n_C} \\
c_{21,n_C} & \cdots & c_{2m,n_C} \\
  \vdots & \ddots & \vdots \\
c_{m1,n_C} & \cdots & c_{mm,n_C}
\end{bmatrix}
\begin{bmatrix}
  \epsilon_{1,k-n_C} \\
  \epsilon_{2,k-n_C} \\
  \vdots \\
  \epsilon_{m,k-n_C}
\end{bmatrix}
\]
Generalizing univariate models to multivariate ones is trivial, since it only requires expression in terms of vectors and matrices. Using vector and matrix notations, the VARMA($n_A, n_C$) in (4.11) can be written as:

$$y_k = \sum_{i=1}^{n_A} A_i y_{k-i} + \sum_{i=1}^{n_C} C_i \epsilon_{k-i} + \epsilon_k$$

(4.12)

where the system output and the noise vectors are $y_k = [y_{1,k} \ldots y_{m,k}]^T$ and $\epsilon_k = [\epsilon_{1,k} \ldots \epsilon_{m,k}]^T$, respectively. In (4.12), the $A_i$ and $C_i$ are $m \times m$ matrices composed of model parameters:

$$A_i = \begin{bmatrix} a_{11,i} & \cdots & a_{1m,i} \\ \vdots & \ddots & \vdots \\ a_{m1,i} & \cdots & a_{mm,i} \end{bmatrix}, \quad C_i = \begin{bmatrix} c_{11,i} & \cdots & c_{1m,i} \\ \vdots & \ddots & \vdots \\ c_{m1,i} & \cdots & c_{mm,i} \end{bmatrix}$$

(4.13)

Similarly, time-series data that contains $r$-input and $m$-output variables can be described with VARMAX($n_A, n_B, n_C$) model:

$$y_k = \sum_{i=1}^{n_A} A_i y_{k-i} + \sum_{i=0}^{n_B} B_i u_{k-i-1} + \sum_{i=1}^{n_C} C_i \epsilon_{k-i} + \epsilon_k$$

(4.14)

where input vector $u_k = [u_{1,k} \ldots u_{r,k}]^T$ and $B_i$ are $m \times r$ matrices:

$$B_i = \begin{bmatrix} b_{11,i} & \cdots & b_{1r,i} \\ \vdots & \ddots & \vdots \\ b_{m1,i} & \cdots & b_{mr,i} \end{bmatrix}$$

(4.15)

Equation (4.14) can also be expressed in terms of matrix polynomials:
\[ A(q^{-1}) y_k = B(q^{-1}) u_{k-1} + C(q^{-1}) \epsilon_k \]  

(4.16)

where

\[ A(q^{-1}) = I_{m \times m} - A_1 q^{-1} - \ldots - A_n q^{-n_A} \]

\[ B(q^{-1}) = B_0 + B_1 q^{-1} + \ldots + B_n q^{-n_B} \]  

(4.17)

\[ C(q^{-1}) = I_{m \times m} + C_1 q^{-1} + \ldots + C_n q^{-n_C} \]

4.3 Criterion for Model Type and Order Selection

Selection of appropriate model type and order is an important step for any modeling technique. Sometimes, for a given time-series data set, there can be multiple models that adequately represent the data. In the literature, numerous criteria have been introduced for the best model selection among a range of potential models of different orders or types that fit a given data set. In general, the proposed criteria can be divided into two groups: (i) criteria that are based on statistics from residuals of the fitted model, and (ii) criteria that are based on forecast that evaluates the one-step-ahead prediction error. Residuals based approaches include the Likelihood Ratio (LR) test, Akaike information criterion (AIC), Bayesian estimation method, Schwarz test, and Hannan-Quinn criterion test. Final prediction error and autoregressive transfer function tests are examples for the forecast error based methods [91]. Among these criteria, the AIC is the most widely used approach, and it has become a standard tool for time series model fitting.

The AIC is an extension of the LR test to include an additional penalty on the total number of model parameters [92], and [93]. The AIC criterion is expressed as:
\[ AIC = -2 \ln(\text{maximum likelihood}) + 2M \] (4.18)

where the first term is the value of the maximum likelihood function evaluated at the parameter estimates, and \( M \) is the total number of parameters in the model. For a model developed from total of \( N \) number of observations, the log-likelihood function, \( \ln(L) \), is defined by:

\[ \ln(L) = -\frac{N}{2} \ln(2\pi\sigma_e^2) - \frac{1}{2\sigma_e^2} S(\hat{\theta}) \] (4.19)

where

\[ S(\hat{\theta}) = \sum_{i=1}^{N} e_i^2 \] (4.20)

is the square sum of the residual terms. \( \hat{\theta} \) denotes the estimated model parameters. The residuals are independent and identically distributed (i.i.d.) variables with \( N(0,\sigma_e^2) \), and \( S(\hat{\theta})/N = \sigma_e^2 \). By maximizing (4.19) with respect to \( \hat{\theta} \) and \( \sigma_e^2 \), the first term of AIC in (4.18) is obtained as [94]:

\[ \ln(\text{maximum likelihood}) = -\frac{N}{2} \ln(\sigma_e^2) - \frac{N}{2} \left[ 1 + \ln(2\pi) \right] \] (4.21)

The last term in (4.21) is constant; hence, the AIC test in (4.18) reduces to the minimization of:

\[ AIC = N \ln(\sigma_e^2) + 2M \] (4.22)

A model with lower AIC is considered to be a better model. In (4.22), the first term is a measure for fit of the model, while the second term is the penalty factor for inclusion of additional parameters to the model. The AIC rewards goodness-of-fit of a model to data, but with a trade-off for over-parameterization.

### 4.4 Identification of Model Parameters

Recursive least squares (RLS) algorithm is a powerful tool for online identifi-
cation, and for tracking time-varying model parameters. For a given model-order and type, the RLS provides the estimate of model parameters that minimize the squared error between the observed and estimated variables.

Any type of time-series models can easily be rewritten in the following linear regression form:

\[ y_k = \varphi_k^T \hat{\theta}_{k-1} + e_k \]  

(4.23)

where \( y_k \) represents the actual observation of the system at the \( k \)th sampling instant, and \( e_k \) is defined as deviation (or error) between the observed system output, \( y_k \), and its model estimated value, \( \hat{y}_k \):

\[ e_k = y_k - \hat{y}_k = y_k - \varphi_k^T \hat{\theta}_{k-1} \]  

(4.24)

In (4.23) and (4.24), \( \varphi_k \) represents the vector of historical observations, and \( \hat{\theta}_{k-1} \) is a vector that contains the estimates of the time-varying model parameters. For instance, for a system represented with ARMAX(\( n_A, n_B, n_C \)) model in (4.7), \( \varphi_k \) and \( \hat{\theta}_{k-1} \) are given by:

\[ \varphi_k = \begin{bmatrix} y_{k-1} & \ldots & y_{k-n_A} & u_{k-1-d} & \ldots & u_{k-n_B-1-d} & e_{k-1} & \ldots & e_{k-n_C} \end{bmatrix}^T \]  

(4.25)

\[ \hat{\theta}_{k-1} = \begin{bmatrix} \hat{a}_{1,k-1} & \ldots & \hat{a}_{n_A,k-1} & \hat{b}_{0,k-1} & \ldots & \hat{b}_{n_B,k-1} & \hat{c}_{1,k-1} & \ldots & \hat{c}_{n_C,k-1} \end{bmatrix}^T \]  

(4.26)

In (4.25), the unknown noise sequence \( \{ \epsilon_k \} \) in the ARMAX model of (4.7) is replaced by the estimated prediction error series \( \{ e_k \} \) defined in (4.24). Representation of the vectors \( \varphi_k \) and \( \hat{\theta}_{k-1} \) for any other time-series model type is straightforward.

Weighted RLS method is an extension of RLS algorithm to include a forgetting factor, \( \lambda \). The weighted RLS approach requires identification of the model parameter estimates, \( \hat{\theta}_k \), that minimize the weighted cumulative square of the residuals \( e_k \) defined
in (4.24):

\[ V_k(\hat{\theta}) = \sum_{i=1}^{k} \lambda^{k-i} e_k^2 \]  

(4.27)

For \( \lambda = 1 \), the algorithm reduces to RLS. The forgetting factor, \( 0 < \lambda \leq 1 \), puts relative weight on the residuals \( \{e_k\} \). When \( \lambda = 1 \), all deviations from the true data are equally weighted (i.e., infinite memory). On the other hand, small values of \( \lambda \) give more weight on recent observations and the information in previous data is quickly discarded (i.e., short memory).

The weighted RLS algorithm that provides model parameter estimates at each sampling step is given by:

\[
\hat{\theta}_k = \hat{\theta}_{k-1} + K_k e_k = \hat{\theta}_{k-1} + K_k [y_k - \varphi_k^T \hat{\theta}_{k-1}] 
\]  

(4.28)

\[
K_k = \frac{P_{k-1} \varphi_k}{\lambda + \varphi_k^T P_{k-1} \varphi_k} 
\]  

(4.29)

\[
P_k = \frac{1}{\lambda} \left[ P_{k-1} - \frac{P_{k-1} \varphi_k \varphi_k^T P_{k-1}}{\lambda + \varphi_k^T P_{k-1} \varphi_k} \right] 
\]  

(4.30)

\( K_k \) and \( P_k \) in (4.29) and (4.30) stand for the vector of estimator gains and the estimate of error variance matrix, respectively.

### 4.5 Change Detection

The weighted RLS algorithm introduced in Section 4.4 will normally provide improved model tracking and numerical performance with a constant forgetting factor, \( \lambda \), unless the system deviates from its steady state operating conditions. However, for some systems, as is with glucose dynamics, normal operating conditions may include large transition periods. In order to obtain quick model tracking under such deviations, a small value of \( \lambda \) is required. A small \( \lambda \) ensures that the new information
about the system dynamics is quickly collected and the old information is discarded. On the other hand, when the system returns to its near steady state conditions, the small $\lambda$ will lead to increase in error variance, $P$ in (4.30), which in time may cause numerical instability. Therefore, for a system with changing operating conditions, using a constant $\lambda$ in the weighted RLS algorithm is not proper. Instead, a variable $\lambda$ that is assigned a small value during transition periods and a large value during stationary conditions should be preferred.

Since glucose dynamics of a patient with diabetes show great variability and include large deviations from stable fasting conditions on a daily basis, a variable forgetting factor is used in this thesis. The mechanism for varying the $\lambda$ is based on a change detection strategy integrated to the RLS algorithm, that monitors the variation in the model parameters. When the algorithm detects a change in the model parameters, the value of forgetting factor in the RLS is reduced, in order to ensure faster convergence to new model parameters and quick data tracking. The proposed change detection method is described by null and alternative hypotheses given by:

$$H_0 : \ E(\hat{\theta}_k) = \hat{\theta}_N, \ for \ N < k < N + N_W$$

$$H_1 : \ E(\hat{\theta}_k) \neq \hat{\theta}_N, \ for \ N < k < N + N_W$$  \hspace{1cm} (4.31)

In (4.31), $E(\hat{\theta}_k)$ describes the expected value of parameter estimates at the $k$th sampling time. $\hat{\theta}_N$ denotes the vector of unbiased parameter estimates computed by the RLS algorithm using the data until time instant $N$, and $N_W$ is the window size. To avoid changes due to non-persistent abnormalities in the data such as sensor noise, the value of $\lambda$ is not reduced at the first instant of change detection. Instead, consistency of the change for several time steps (i.e., $N_W$) is assured first. When a persistent change that lasts the duration of the window size is detected, $\lambda$ is reduced to a smaller value and $\hat{\theta}_N$ is replaced with its new estimate.
4.6 \( n \)-steps-ahead Prediction

Forecasting with time-series models find broad application in control, optimization or production planning of industrial processes, as well in economic and business planning. Time-series models can be used to predict future values of the variable of interest. Predicted values are computed from current and past observations, to provide minimum mean square of deviation between the actual and forecast values.

The \( n \)-steps-ahead predicted observation is denoted by \( \hat{y}_{k+n|k} \). The \( n \)-steps-ahead predictor can be calculated by succession of \( k \) one-step-ahead predictors. However, a direct method is of more practical interest. Assuming that a given time-series data is best described with an ARMA\((n_A, n_C)\) model, using (4.4) the model can be rearranged as:

\[
y_{k+n} = \frac{C(q^{-1})}{A(q^{-1})} \epsilon_{k+n}
\]

(4.32)

The polynomials in (4.32) can be truncated at the power of \( q^{-n} \), to obtain:

\[
y_{k+n} = F(q^{-1}) \epsilon_{k+n} + \frac{G(q^{-1})}{A(q^{-1})} \epsilon_{k+n} = F(q^{-1}) \epsilon_{k+n} + \frac{G(q^{-1})}{A(q^{-1})} \epsilon_k
\]

(4.33)

where the polynomial \( F(q^{-1}) \) is of order \((n-1)\):

\[
F(q^{-1}) = 1 + f_1 q^{-1} + \ldots + f_{n-1} q^{-n+1}
\]

(4.34)

In (4.33), polynomials \( F(q^{-1}) \) and \( G(q^{-1}) \) must satisfy the following Diophantine equation:

\[
C(q^{-1}) = A(q^{-1}) F(q^{-1}) + q^{-n} G(q^{-1})
\]

(4.35)

which defines the order of polynomial \( G(q^{-1}) \) as \((m+1)\) with \( m = max(n_A, n_C - n + 1, 1) \). In (4.33), the first term, \( F(q^{-1}) \epsilon_{k+n} \), contains future errors that are independent
of $y_k$; hence, after dropping this term, the $n$-steps-ahead prediction can be expressed as:

$$
\hat{y}_{k+n|k;\hat{\theta}} = \frac{G(q^{-1})}{A(q^{-1})} \epsilon_k
$$

(4.36)

Substituting $\epsilon_k = A(q^{-1})/C(q^{-1}) y_k$, (4.36) can be expressed in terms of $y_k$:

$$
\hat{y}_{k+n|k;\hat{\theta}} = \frac{G(q^{-1})}{C(q^{-1})} y_k
$$

(4.37)

At each sampling step, first, the model parameters are identified using the weighted RLS. With known parameter values, the current estimates of polynomials $A(q^{-1})$ and $C(q^{-1})$ are used in (4.35) to obtain the polynomial $G(q^{-1})$ which is then used to compute the $n$-steps-ahead predictor given in (4.37).

Estimation of $n$-steps-ahead predictor, $\hat{y}_{k+n|k;\hat{\theta}}$, for other types of time-series models follows the same procedure. For instance, for the ARMAX model in (4.7), the $n$-steps-ahead predictor is expressed as:

$$
\hat{y}_{k+n|k;\hat{\theta}} = \frac{G(q^{-1})}{C(q^{-1})} y_k + \frac{\Gamma(q^{-1})}{C(q^{-1})} u_{k-1} + E(q^{-1}) u_{k+n-1}
$$

(4.38)

where the polynomials $G(q^{-1})$, $\Gamma(q^{-1})$ and $E(q^{-1})$ are computed using (4.35) and the following Diophantine equation:

$$
F(q^{-1}) B(q^{-1}) = E(q^{-1}) C(q^{-1}) + q^{-n} \Gamma(q^{-1})
$$

(4.39)

4.7 Prediction Performance Analyses

Prediction performance of a model is generally evaluated in terms of deviation of predicted values from the observed data. In this research, relative absolute deviation and sum of squared error are utilized to quantitatively measure the error
in glucose predictions. Both of these performance metrics possess limited clinical implication. Therefore, continuous glucose Clarke error grid analysis (CG-EGA) is also employed to assess the clinical significance of the error in glucose predictions.

4.7.1 Error in Glucose Predictions. Performance of the time-series models developed is evaluated in terms of error in glucose predictions. A common metric is the relative absolute deviation ($RAD$), which is expressed as absolute value of each prediction error divided by the corresponding glucose observation:

$$RAD(\%) = \left| \frac{y_k - \hat{y}_k}{y_k} \right| \times 100 \quad (4.40)$$

Another metric is the sum of squares of the glucose prediction error ($SSGPE$):

$$SSGPE(\%) = \sqrt{\frac{\sum (y_k - \hat{y}_k)^2}{\sum y_k^2}} \times 100 \quad (4.41)$$

In (4.40) and (4.41), $y_k$ denotes the actual glucose measurement (i.e., data), and $\hat{y}_k$ is the model predicted glucose concentration. Note that for $n$-steps-ahead prediction, $\hat{y}_k$ is actually calculated at the $(k - n)$th sampling instant (i.e., $n$-steps before the current time), and its computation does not include glucose measurement information of the last $n$-steps (see Section 4.6). The summation terms in (4.41) are over total number of observations in the data.

The $SSGPE$ is a metric similar to the root mean squared error, $RMSE$. It gives more penalty to larger deviations (i.e., squared deviation) compared to smaller ones. $SSGPE$ and $RAD$ do not depend on data magnitude (i.e., number of observations), since they are normalized by actual glucose measurements.

4.7.2 Continuous Glucose Clarke Error Grid Analysis (CG-EGA). Continuous glucose error grid analysis was originally introduced as a method to evaluate
the clinical accuracy of the measurements from a CGM sensor. The method examines precision in terms of both point-glucose observations, and the direction and rate of glucose change. It accounts for the dependency of successive observations by combining point accuracy with rate accuracy. The CG-EGA can also be used for comparing the model estimated glucose concentrations with their corresponding reference values, and therefore, it can be utilized as a tool to measure a model’s prediction performance.

The CG-EGA consists of separate point and rate precision computations, which are then combined to assess a single accuracy index for each of the hypoglycemic, normoglycemic, and hyperglycemic glucose ranges. The method handles the measurement or prediction errors with regard to their clinical significance. Figure 4.1 illustrates the scatter plots of both point and rate error-grid analyses. Both error-grid plots are divided into several zones to represent clinical implications of the error. The accurate A zones occur around the main diagonal which indicates a perfect fit. The B benign-error zones define errors that will not lead to inaccurate clinical interpretation or treatment, while the C over-correction zones signify that the error can lead to overtreatment. D and E demonstrate the failure-to-detect and the erroneous-prediction zones, respectively. Results of point-EGA and rate-EGA analysis are combined to form a CG-EGA error matrix (e.g., Table 6.7). The error-matrix is divided into three parts to reflect the individual performance analysis for hypoglycemia (i.e., $BG \leq 70 \text{ mg/dl}$), normoglycemia (i.e., $70 \text{ mg/dl} < BG \leq 180 \text{ mg/dl}$) and hyperglycemia (i.e., $BG < 180 \text{ mg/dl}$). In the error matrix, predicted values are considered clinically accurate if they fall into A or B zones of both point-EGA and rate-EGA. Benign errors are defined with acceptable point-EGA accuracy (A or B zones) and significant error in rate-EGA (C, D, or E zones). Erroneous predictions that can lead to negative clinical action occur when significant error in both point-EGA and rate-EGA is detected.
Figure 4.1. Scatter plots for CG-EGA. (a) Point-EGA, and (b) Rate-EGA. l, lower; u, upper.
The components of the proposed control algorithm for closed-loop regulation of blood glucose concentrations are introduced in this chapter. An adaptive control strategy is developed to keep a patient’s glucose concentrations within normoglycemic range and dynamically respond to glycemic disturbances. The model-based control algorithm developed utilizes the linear subject-specific models introduced in Chapter 4 to predict the patient’s future glucose excursions. The required insulin infusion rate is then computed to minimize the deviation of the predicted glucose values from a reference glucose trajectory. The closed-loop algorithm focuses on subcutaneous route for both glucose sensing and insulin delivery, and therefore, it is designed to account for the time-delay between blood glucose (i.e., controlled variable) and subcutaneous glucose (i.e., measured variable) concentrations, and the additional delay in insulin action due to its slow subcutaneous absorption. The algorithm developed is also designed to function in a fully automated manner and does not require disturbance announcements or patient-specific tailoring.

In this chapter, first, the challenges of closed-loop blood glucose regulation are discussed. Then, the components of the control algorithm developed are individually described.

5.1 Challenges

Closing the loop for blood glucose regulation has been an active research area for decades and a wide-range of control algorithms have been proposed (see Section 3.2). Still, the development of a commercial fully automated closed-loop system remains a challenge. One of the critical limitations is the short life-time and reliability issues of the currently available continuous glucose sensors that are discussed in Sec-
tion 1.4.1. However, development of a reliable CGM technology is a very extensive research area, and it is widely believed that this limitation will be solved in the near future. In this thesis, the availability of a reliable continuous glucose sensor and an insulin pump is assumed, and the focus is on the development of a control algorithm that connects these two devices and provides fully automated blood glucose regulation.

Another challenge is the wide inter-subject variability of glucose-insulin dynamics. A reliable closed-loop system should be able to account for inter-subject variability and also adapt to daily variations of a subject’s glucose metabolism. We overcome this limitation with the use of subject-specific modeling strategy introduced in Chapter 4.

Patients with diabetes are also exposed to external glycemic disturbances (e.g., meal and exercise) that cause large glucose fluctuations on a daily basis. Rejection of glycemic disturbances such as meal or exercise can easily be achieved by disturbance modeling when information about the meal size or exercise intensity is available. However, it will require the burden for patients to enter manual inputs on a daily basis which also increases the potential for human errors. The closed-loop algorithm developed in this thesis does not require such patient intervention or any disturbance announcements.

When subcutaneous insulin delivery and subcutaneous glucose sensing are considered, two time delays are also introduced to the glucose control problem. The first is the slow insulin absorption from the adipose tissue that leads to delay in input (i.e., insulin) action. The second is the time-delay between the controlled (i.e., blood glucose) and the measured (i.e., subcutaneous glucose) variables. In this thesis, two time-delay compensators are integrated to the proposed closed-loop algorithm in order to cope with these challenges.
5.2 Delay Compensators

Two time-delay compensators are introduced to the closed-loop algorithm developed: (i) a lag-filter that is designed to estimate blood glucose concentrations from subcutaneous glucose readings, and (ii) a Smith predictor type structure that explicitly defines the time-delay due to the subcutaneous insulin absorption.

5.2.1 Lag-Filter. Subcutaneous space appears to be the minimally invasive site for glucose measurement, and therefore, is the most preferred site by the CGM devices currently available in the market. Subcutaneous glucose sensors provide measurements from the interstitial fluid (i.e., subcutaneous). However, diagnosis and management of diabetes is defined in terms of blood glucose (not subcutaneous) concentration by clinicians, and the standard criterion for control of the disease is still the blood glucose regulation. Therefore, a control algorithm using subcutaneous glucose measurements should account for the time-lag between subcutaneous and blood glucose concentrations.

The dynamics between subcutaneous and blood glucose concentrations has been modeled with a two-compartmental material balance model in the literature [95]:

\[
V \frac{dG_{subc, meas}}{dt} = k_m A (G_{blood} - G_{subc, meas}) - V k_r G_{subc, meas}
\]

(5.1)

In (5.1), \(V\) is the sensing volume, \(k_m\) is the mass transfer coefficient, and \(A\) is the surface area of the sensing volume. \(k_r\) is the rate constant for glucose uptake in the subcutaneous compartment, and \(k_r \approx 0\) is reported by [95]. The original model of (5.1) is be reduced to:

\[
\frac{dG_{subc, meas}}{dt} = \frac{1}{\tau} G_{blood} - \frac{1}{\tau} G_{subc, meas}
\]

(5.2)
where \( \tau = V/k_m A \). The time constant, \( \tau \), has units of min and reflects the time-lag in subcutaneous glucose readings relative to blood glucose concentrations.

Similar material balance models have been proposed by [96] and [97]. Even tough, the time constant depends on sensor specifications and the measurement site, [95], [98] and [99] have shown that \( \tau \) is relatively constant for a specific CGM device and insertion site.

Taking the Laplace transform of (5.2), the relationship between subcutaneous and blood glucose concentrations is described by the following low-pass (first-order lag) filter:

\[
\frac{G_{\text{subc,meas}}(s)}{G_{\text{blood}}(s)} = \frac{a}{s + a}
\]

where \( a = 1/\tau \) and \( s \) is the Laplace variable. The continuous filter described by (5.3) is then converted to a digital filter using z-transformation method [100].

Finally, the low-pass digital filter is integrated to the closed-loop structure as depicted in Figure 5.1. Blood glucose concentrations are estimated from subcutaneous glucose readings using the lag-filter, and these estimated values are then used in the control algorithm to compute the required insulin infusion rates that will keep the blood glucose concentrations within the desired range.

5.2.2 Smith Predictor. Depending on insulin administration site (e.g., intravenous, intraperitoneal, or subcutaneous) and insulin type (e.g., rapid-, short-, intermediate-, or long-acting), time-delays of different lengths exist between the insulin delivery time and its first effect on blood glucose levels. In this thesis, a Smith predictor type structure is used to deal with such time-delay in the control action (i.e., insulin).

The Smith predictor [101] is a well-known strategy proposed for dead-time
compensation for plants with large time delays. As shown in Figure 5.2, it introduces an inner feedback loop that consists of a model that ignores the time-delay in the plant (i.e., $G$) and a pure time-delay element (i.e., $q^{-d}$). The process model without the time-delay is used to predict the effect of current control action on the controlled variable $d$-steps ahead. Predicted process output is also delayed $d$-steps for comparison with the current actual output which provides correction for disturbance signals or modeling errors.

5.3 Model

Under closed-loop conditions, the effect of insulin delivered is also included in the time-series model, and the ARIMAX model structure defined by (4.10) with $p = 1$ (i.e., $\nabla^p z_k = z_k - z_{k-1} = \Delta z_k$) is selected:

$$A(q^{-1}) \Delta y_k = q^{-d} B(q^{-1}) \Delta u_{k-1} + C(q^{-1}) \epsilon_k$$  (5.4)
Figure 5.2. Smith predictor structure used for (a) GPC strategy, and (b) LQC strategy.
In (5.4), \( y_k \) and \( u_k \) represent the glucose concentration and the insulin infusion rate at the \( k \)th sampling step, respectively. Model parameters of (5.4) are identified using the weighted RLS and change detection methods described in Chapter 4. The ARIMAX model in (5.4) is rewritten in the regression form of (4.23) and (4.24), where the vectors of past observations, \( (\varphi_k) \), and model parameter estimates, \( (\hat{\theta}_{k-1}) \), are given by:

\[
\varphi_k = [\Delta y_{k-1} \Delta y_{k-2} \cdots \Delta y_{k-n_A} \Delta u_{k-d-1} \Delta u_{k-d-2} \cdots \Delta u_{k-d-n_B} \epsilon_{k-1} \epsilon_{k-2} \cdots \epsilon_{k-n_C}]^T
\]
\[
(5.5)
\]

\[
\hat{\theta}_{k-1} = \begin{bmatrix} \hat{a}_{1,k-1} \hat{a}_{2,k-1} \cdots \hat{a}_{n_A,k-1} \hat{b}_{0,k-1} \hat{b}_{1,k-1} \cdots \hat{b}_{n_B,k-1} \hat{c}_{1,k-1} \hat{c}_{2,k-1} \cdots \hat{c}_{n_C,k-1} \end{bmatrix}^T
\]
\[
(5.6)
\]

The identified ARIMAX model is then used in a model-based control algorithm to compute the required control action.

## 5.4 Control Law

For the computation of the optimum control action (i.e., insulin delivery rate), two well-known model-based control strategies, the generalized predictive control (GPC) and the linear quadratic control (LQC), are used and modified to include the two delay compensators discussed in Section 5.2 and a time-varying reference glucose trajectory introduced in Section 5.5.

### 5.4.1 Generalized Predictive Control

GPC provides the optimum control action that is computed by minimization of the following quadratic cost function:

\[
J(N_y, N_u) = \sum_{j=1}^{N_y} q [\hat{y}_{k+j|k} - y_{ref,k+j}]^2 + \sum_{j=1}^{N_u} r [\Delta u_{k+j-1}]^2
\]
\[
(5.7)
\]

In (5.7), \( \hat{y}_{k+j|k} \) and \( y_{ref,k+j} \) represent \( j \)-steps-ahead predicted process output
(i.e., glucose concentration) and desired reference trajectory, respectively. $\Delta u_k$ is the incremental control input (i.e., insulin delivery rate) at the $k$th sampling step, and $\Delta u_k = u_k - u_{k-1}$. Output prediction horizon ($N_y$), control horizon ($N_u$), and weights on output deviation and incremental input ($q$ and $r$ respectively) are the controller design parameters. $N_u \leq N_y$ is used and for $i \geq N_u$, $\Delta u_{k+i} = 0$ is assumed.

The optimization of (5.7) requires the estimation of $j$-steps-ahead predicted glucose values, $\hat{y}_{k+j|k}$. Predicted values are calculated using the ARIMAX model in (5.4) after solving for the following Diophantine equation:

$$C = E_j A \Delta + q^{-j} F_j$$

(5.8)

For a simplified representation, the backward shift operator ($q^{-1}$) is dropped from the polynomial notations in (5.8), and $\Delta$ represents $(1 - q^{-1})$. $E_j$ and $F_j$ are polynomials with orders $(j - 1)$ and $n_A$ respectively. Using (5.4) and (5.8), one can solve for $\hat{y}_{k+j|k}$ as a function of future control actions, past input and past output variables [102]:

$$\hat{y}_{k+j|k} = G_j \Delta u_{k+j-1} + \Gamma_j \Delta u_{k-1} + F_j y_k^f$$

(5.9)

In (5.9), $\Delta u_k^f = (1/C) \Delta u_k$ and $y_k^f = (1/C) y_k$, and the polynomials $G_j$ and $\Gamma_j$ are defined from a second Diophantine equation (i.e., $H_j = G_j C + q^{-j} \Gamma_j$ with $H_j = E_j B$). Using (5.9), future estimations over the entire prediction horizon can then be expressed in a vector notation as:

$$\hat{y} = G \hat{u} + \hat{f}$$

(5.10)

where

$$\hat{y} = [\hat{y}_{k+1|k} \hat{y}_{k+2|k} \ldots \hat{y}_{k+N_y|k}]^T$$

(5.11)
\[ \tilde{u} = [\Delta u_k \Delta u_{k+1} \ldots \Delta u_{k+N_u-1}]^T \]  
\quad (5.12)

The vector \( \tilde{u} \) is defined as free response predictions and includes the last two terms of (5.9), which is a function of past input and past output variables. Substituting (5.10) into (5.7), the cost function is solved to give the vector of future optimum control actions:
\[ \tilde{u} = (G^T G + \lambda I)^{-1} G^T (y_{\text{ref}} - f) \]  
\quad (5.13)

with \( \lambda = \tau / q \). Only the first element of the input sequence is implemented, and at the next sampling step, the optimization procedure is repeated.

**Modification to GPC to Include Unmeasured Control Variable (Lag-Filter):** As previously discussed, the control problem at hand is one where the unmeasured auxiliary controlled variable (i.e., blood glucose) needs to be estimated from a measurable output (i.e., subcutaneous glucose). The auxiliary controlled variable, \( \psi_k \), can be defined in terms of measured output, \( y_k \), by a user-specified transfer function as:
\[ \psi_k = P(q^{-1}) y_k \]  
\quad (5.14)

with \( P = P^n / P^d \). The numerator and the denominator terms of polynomial \( P \) are described by \( P^n \) and \( P^d \), respectively. For a given \( \tau \) value, \( P(q^{-1}) \) is the digital (i.e., z-transform) equivalent of the continuous filter defined in (5.3). Regulation of the auxiliary output is then achieved by optimization of the following quadratic cost function:
\[ J(N_y, N_u) = \sum_{j=1}^{N_y} q \left[ \hat{\psi}_{k+j|k} - \psi_{\text{ref},k+j} \right]^2 + \sum_{j=1}^{N_u} r \left[ \Delta u_{k+j-1} \right]^2 \]  
\quad (5.15)

To solve (5.15), the regular GPC algorithm of (5.8)-(5.13) needs to be modified to forecast \( \hat{\psi}_{k+j|k} \) values instead of \( \tilde{y}_{k+j|k} \). The procedure is simple as only replacement of \( y_k \) with \( \psi_k = P y_k \) is required. For instance, the Diophantine expression in (5.8)
becomes \( P C = E_j A \Delta + q^{-j} F_j/P^d \), and (5.9) is expressed as \( \hat{\varphi}_{k+j|k} = G_j \Delta u_{k+j-1} + \Gamma_j \Delta u_{k-1} + F_j y_k^f/P^d \) where \( \Delta u_k^j = (1/C P^n) \Delta u_k \) and \( y_k^f = (1/C P^n) y_k \).

**Modification to GPC to Account for Delayed-Input (Smith Predictor Type Structure):** To improve the robustness in the case of delays in the input, the Smith predictor type structure shown Figure 5.2(a) is introduced into the GPC strategy. GPC can intrinsically handle and compensate for the dead-time in a process. However, the optimal predictor defined in (5.9) or (5.10) does not allow for analysis of the effect of dead-time in a closed-loop system. Differently, by separating the solution of Diophantine equation into two sets (i.e., from \( j = 1 : d \) and \( j = d + 1 : d + N_y \)), the future predictions of the auxiliary variable are expressed as:

\[
\begin{bmatrix}
\hat{\psi}_{k+d+1|k} \\
\hat{\psi}_{k+d+2|k} \\
\vdots \\
\hat{\psi}_{k+d+N_y|k}
\end{bmatrix} = S_1 
\begin{bmatrix}
\Delta u_k \\
\Delta u_{k+1} \\
\vdots \\
\Delta u_{k+N_y-1}
\end{bmatrix} + S_2 
\begin{bmatrix}
\Delta u_{k-1} \\
\Delta u_{k-2} \\
\vdots \\
\Delta u_{k-n_B}
\end{bmatrix} + S_3 
\begin{bmatrix}
\hat{\psi}_{k+d+1|k} \\
\hat{\psi}_{k+d+2|k} \\
\vdots \\
\hat{\psi}_{k+d+n_A|k}
\end{bmatrix}
\]

which makes the effect of dead-time to be explicitly included to the predictor structure [103]. Compared to (5.10), the free response term of (5.16) requires future predictions of the output from \( j = 1 : d \), which are computed using the open-loop model of the plant with correction to include mismatch between the output and predictions due to modeling errors or disturbance signals (i.e., \( \hat{\psi}_{k+d|k} = G u_k + [\psi_k - G q^{-d} u_k] \) using notation of Figure 5.2(a)). Structure of (5.16) does not alter the nominal controller performance compared to the general GPC, and it allows improved performance for processes with dead-time which can be handled independently from the controller design [104].

**Constraints:** In addition to the modifications of the regular GPC to include an
auxiliary output (i.e., blood glucose concentration) and a control structure to accommodate for dead-time in the input, constraints are also imposed to the optimization problem due to technical restrictions of insulin pumps and drug safety limitations. The control law is then calculated by solving the following constrained quadratic programming (QP) problem:

\[
\min_u \ J(N_y, N_u) = \sum_{j=d}^{N_y+d} q \left[ \hat{\psi}_{k+j|k} - \psi_{ref,k+j} \right]^2 + \sum_{j=1}^{N_u} \left[ \Delta u_{k+j-1} \right]^2 \\
\text{such that} \quad u_{\min} \leq u_k \leq u_{\max}
\]

\[|\Delta u_k| \leq \Delta_{\max}\]

Limits on infusion rate (i.e., amplitude constraint) are introduced due technical restrictions (e.g., \(0 \text{ U/h} \leq u_k \leq 4.02 \text{ U/h}\)) and a constraint on rate of control action is included to avoid infusion of an excessive amount of insulin at any time (e.g., \(\Delta_{\max} = u_{\max}/3\)).

5.4.2 Linear Quadratic Control. LQC provides optimal control action that minimizes the following infinite horizon quadratic cost function:

\[
J = \sum_{k=0}^{\infty} \left( x_k^T Q x_k + u_k^T R u_k \right) \\
\]

which is subject to system dynamics represented by the following discrete-time state space system:

\[
x_{k+1} = G x_k + H u_k \\
y_k = F x_k + w_k
\]
In (5.18) and (5.19), the vector \( x_k \) is the state variable, \( u_k \) is the input (i.e., insulin infusion rate), \( y_k \) is the output (i.e., glucose concentration), and \( w_k \) is the measurement noise at the \( k \)th sampling step. \( Q \) is the diagonal state weighting matrix (assumed to be positive semidefinite \( Q \geq 0 \)) and \( R \) is the diagonal input weighting matrix (assumed to be positive definite \( R > 0 \)). The pair \((G, H)\) is assumed to be stabilizable. The state space model matrices \( G, H, \) and \( F \) are obtained from the minimum state space realization (e.g., observable canonical state space realization) of the identified ARIMAX time-series model at each sampling step.

Solution for optimization of (5.18) subject to (5.19) is given by the following linear state feedback control law:

\[
    u_k = -K \hat{x}_k
\]

where \( \hat{x}_k \) is the optimal (i.e., Kalman) estimate of process states \( x_k \), and the state feedback gain \( K \) is defined by:

\[
    K = (R + H^T PH)^{-1} H^T P G
\]

In (5.21), \( P \) is calculated by solving for the following discrete Riccati equation:

\[
    P = Q + G^T P G - G^T P H (R + H^T P H)^{-1} H^T P G
\]

Modification to LQC to Include Unmeasured Control Variable (Lag-Filter):

Introducing the auxiliary output (i.e., blood glucose), \( \psi_k \) in (5.14), the ARIMAX model in (5.4) is rearranged as:

\[
    (P^d A \Delta) \psi_k = q^{-d} (P^n B \Delta) u_{k-1} + (P^n C) \epsilon_k
\]
State space model matrices $G$, $H$ and $F$ in (5.19) are then identified by state space realization of (5.23) instead of (5.4), and $y_k$ is replaced with $\psi_k$.

Modification to LQC to Account for Delayed-Input (Smith Predictor Type Structure): With the regular LQC formulation, the state space system in (5.19) possesses one-step delay in the input. However, when blood glucose regulation is considered, a larger delay may be introduced to the system depending on the site of insulin delivery. Therefore, for systems with large delays, the optimal control action in (5.20) should be modified accordingly. One option is to increase the order of the state space model by $d$ elements, where $d$ is the steps of delay in input action. For instance, the polynomial $B(q^{-1})$ in the ARIMAX model of (5.4) can equivalently be expressed as polynomial $B'(q^{-1})$ with the following parameter vector:

$$
\begin{bmatrix}
0 & 0 & \cdots & 0 & b_0 & b_1 & \cdots & b_n
\end{bmatrix}
$$

(5.24)

The modified model, $(A \Delta)y_k = (B' \Delta)u_{k-1} + C \epsilon_k$, keeps the characteristics of the dead-time-free or regular LQC algorithm (just the dimension of the system is increased), and therefore, the optimal input for the augmented system can be solved using (5.20). The matrices $G$, $H$ and $F$ are state space realization of the modified ARIMAX model with polynomials $(A \Delta)$, $(B' \Delta)$ and $C$.

Another method for dealing with dead-time is to express the state space model as:

$$
\begin{align*}
x_{k+1} &= G x_k + H u_{k-d} \\
y_k &= F x_k + w_k
\end{align*}
$$

(5.25)

where the matrices $G$, $H$ and $F$ are state space realization of (5.4) using the polyno-
mials A, B and C. The optimal control law for this problem is then given by:

$$u_k = -K \hat{x}_{k+d}$$

(5.26)

where the estimates of future states are found from the following expression:

$$\hat{x}_{k+d} = G^d \hat{x}_k + \sum_{j=-d}^{-1} G^{-(j+1)}H u_{k+j}$$

(5.27)

which has a Smith predictor type structure presented in Figure 5.2(b) and discussed in [105] and [106].

### 5.5 Reference Glucose Trajectory

Blood glucose regulation is an asymmetric control problem since the immediate health dangers of hypoglycemia are of greater extent compared to long-term impact of hyperglycemia. A reliable closed-loop algorithm should provide faster recovery from hypoglycemic conditions compared to hyperglycemia. For this reason, an asymmetric and time varying reference glucose trajectory, instead of a single set-point target, is used in this thesis. Several studies suggested a similar approach with an asymmetric control structure, performance objective, or reference trajectory [6], [107], [108], [109].

Figure 5.3 illustrates the reference glucose trajectory used in this thesis, which is similar to the one proposed by Hovorka et al. [6]. Glucose concentration of 80 mg/dl is the ultimate target. For glucose measurements below the target value, an exponentially increasing trajectory is tracked to ensure faster recovery from hypoglycemic conditions. On the other hand, for hyperglycemic glucose readings (i.e., >160 mg/dl) a linearly decreasing trajectory at a rate of 10 mg/dl/step is preferred. This rate is reduced to 5 mg/dl/step for glucose measurements within the 160-80 mg/dl range.

The objective is to avoid any sudden decrease in glucose concentrations that
can be caused by aggressively high insulin infusion rates, and to have a faster response during hypoglycemic conditions. Using a constant desired glucose value as a reference trajectory may result in aggressive input signals, and therefore, overestimated insulin infusion rates, especially when large and sudden changes in glucose concentrations are experienced (e.g., during food consumption). Slow absorption of subcutaneously administered insulin increases the risk of aggressive and overestimated infusion rates that can lead to hypoglycemia. Introducing a time-varying trajectory that depends on current glucose measurement will reduce the aggressiveness of the control action and also provide faster recovery from hypoglycemia.
CHAPTER 6
GLUCOSE PREDICTION WITH UNIVARIATE MODELS - RESULTS

Estimation of future glucose concentrations is a crucial task for diabetes management. With the current therapy, it is generally difficult to estimate future glucose levels and therefore to determine the required corrective action. Reliable glucose prediction models will improve management with diabetes. For instance, predicted glucose values can be used for early hypoglycemic/hyperglycemic alarms or for adjustment of insulin amount/rate.

First part of this thesis focuses on the development of a reliable univariate subject-specific modeling algorithm for predicting a subject’s future glucose concentrations. Individual components of the algorithm are discussed in Chapter 4. The models are developed using a subject’s continuous glucose monitoring (CGM) sensor data. The algorithm estimates future glucose levels using recent history of glucose measurements only, and does not require any prior information about glycemic disturbances such as meal consumption or insulin administration. Availability of a reliable CGM device that provides accurate glucose readings with no missing data points is assumed.

Using a subject’s CGM data, time-series analyses are implemented to develop low-order AR and ARMA models defined in (4.1) and (4.3), respectively. ARMAX models in (4.7) are not considered since the only available observations are for glucose concentration. Model order is selected based on preliminary analyses conducted with time-invariant (i.e., constant parameter) time-series models using hospitalized patient data (Section 6.3). AIC criterion described in Section 4.3 is used for best model order selection. Time-invariant time-series models show slow data-tracking performance for a system such as glucose dynamics that frequently fluctuates from stable fasting conditions. Therefore, for a defined model order and type, the weighted RLS method
described in Section 4.4 is used for online estimation of the model parameters. Model parameters are recursively identified at each sampling step as new data become available to include the most recent glucose dynamics information. In order to improve prediction performance and data tracking in presence of glycemic disturbances, a variable forgetting factor (\(\lambda\)) approach is introduced to the weighted RLS algorithm. The variable \(\lambda\) is implemented with incorporation of a change detection strategy to the proposed algorithm as described in Section 4.5. Change in glucose dynamics is depicted with drastic changes in the identified model parameters. When a change is detected, the algorithm reduces the value of \(\lambda\) in the next sampling step in order to guarantee quick model adaptability to fluctuations in glucose excursions. In this way, good tracking performance is targeted not only during slow frequency changes in glucose dynamics but also during drastic and sudden variations.

The models developed are subject-specific, since they are developed from a patient’s own frequently measured data, and are updated at each sampling step to portray any variation in the patient’s glucose metabolism.

6.1 Algorithm Overview

The proposed univariate glucose prediction algorithm is described step-by-step as follows:

- **Step 0:** Decide on the model structure such as model order and type. Assign the initial values for \(\varphi_1\) in (4.25), \(\hat{\theta}_0\) in (4.26), and \(P_0\) in (4.30).

- **Step 1:** Read the glucose measurement from the CGM device.

- **Step 2:** For the model structure defined at Step 0, identify the model parameters \((\tilde{\theta}_k)\) using the weighted RLS method in (4.28)-(4.30).

- **Step 3:** Check for change detection using (4.31). If a change is detected,
assign a flag and go to Step 4. Otherwise go to Step 5. (Flags are stored for $N_W$ sampling instants).

- **Step 4:** Check if flag was assigned for all of the last $N_W$ steps. If the answer is yes, at the next sampling step, reduce the value of the forgetting factor for one step and replace $\hat{\theta}_N$ in (4.31) with its new estimate. Otherwise, keep the normal values of $\lambda$ and $\hat{\theta}_N$.

- **Step 5:** Calculate the $n$-steps-ahead predicted glucose value using (4.37).

- **Step 6:** Update $\varphi_{k+1}$ in (4.25) to include the new CGM measurement from Step 1, and update $\hat{\theta}_k$ in (4.26) with its new value from Step 2. Then, return to Step 1.

### 6.2 Subject Data

Two separate patient databases collected under (A) disturbance-free (hospitalized) and (B) normal daily life conditions are used to evaluate the univariate modeling algorithm developed. Both databases consist of glucose concentration data collected using a CGM device. The two study procedures were reviewed and approved by the University of Illinois at Chicago Institutional Review Board. Prior to participating in the study, all subjects completed consent and HIPPA documents. Data collection took place at the University’s general clinical research center.

*Study group A:* This study population consisted of healthy individuals (sample size $n = 22$, $43.50 \pm 10.4$ years old, body mass index, BMI = $35.02 \pm 3.4$ kg/m$^2$), glucose-intolerant subjects ($n = 7$, $45.00\pm7.0$ years old, BMI = $34.88\pm4.1$ kg/m$^2$) and subjects with type 2 diabetes ($n = 11$, $47.18\pm5.1$ years old, BMI = $36.80\pm4.1$ kg/m$^2$). Data were originally collected to investigate the effect of moderate intensity exercise (i.e., $30$ min walk on a treadmill performed before breakfast at an intensity of
65% maximal oxygen consumption, $\dot{V}O_{2\text{max}}$, measured with indirect spirometry) on postprandial glucose during two separate randomized protocols (i.e., exercise and non-exercise) [110]. Subjects were hospitalized for 48 h and were prescribed three standard meals for each day. A subject’s glucose concentration was monitored with a CGM system (CGMS System Gold$^\text{TM}$, Medtronic MiniMed, Northridge, CA) for 48 h. In this thesis, the CGMS data collected during the non-exercise protocol is used only.

**Study group B:** This study population consisted of subjects with type 2 diabetes ($n = 14$, 47.93 ± 6.1 years old, BMI = 36.94 ± 4.9 kg/m$^2$) and healthy subjects ($n = 8$, 42.75 ± 12.7 years old, BMI = 34.66 ± 5.8 kg/m$^2$). The database consisted of glucose concentration data collected at 5 min intervals using the CGMS System Gold monitoring device. The subjects wore the CGMS at home for 48 h, with no additional instructions other than how to operate the monitor and calibration techniques of the device.

### 6.3 Preliminary Analysis with Non-Recursive Time-Series Models

Time-series models with constant parameters (i.e., non-recursive model) are examined in this section. With current diabetes therapies, patients are obliged to follow a strict diet and an activity plan each day. Therefore, glucose profiles might show little day-to-day variation for patients with well-controlled diabetes. For such patients, time-invariant models developed from a 24 h glucose profile might provide satisfactory performance for predicting the patient’s glucose fluctuations during any other day.

CGM data of each patient described in Section 6.2 are smoothed using a low-pass filter (filter characteristics are described in Section 6.4) in order to remove any noise in the sensor data. The first half of the smoothed CGM data is used for
development and identification of a linear non-recursive model for each individual subject. Raw CGM data from the second half are then used to validate the models developed and assess their prediction performances.

### 6.3.1 Model Structure

Using a subject’s past glucose observations, univariate time-series models are developed for predicting future glucose levels. Models considered include AR, MA and ARMA structures defined in (4.1), (4.2) and (4.3), respectively. Models of various orders AR\((n_A)\), MA\((n_C)\) and ARMA\((n_A, n_C)\) are examined for each patient individually, by using the MATLAB System Identification Toolbox (MathWorks Inc., Natick, MA). AIC criterion described in Section 4.3 is utilized for best model selection. AIC value of each model is calculated using (4.22), and the model with the lowest AIC value is selected.

Table 6.1 provides the population mean AIC values for AR and MA models of order from one to five. Results are for the patient population with diabetes of study group A described in Section 6.2. Glucose variability is the highest for patients with diabetes, therefore, the population with diabetes demonstrated higher AIC values compared to healthy and glucose-intolerant populations. Results in Table 6.1 reveal that AIC values for AR models are significantly lower than the AIC values for MA models with same order. Therefore, the AR model structure is more suitable to describe the CGM data compared to MA model. Among various orders for AR, \(n_A = 3\) is selected, since it results in the lowest AIC value.

<table>
<thead>
<tr>
<th>Model Type</th>
<th>Model Order ((n_A) or (n_C))</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR((n_A))</td>
<td>1</td>
</tr>
<tr>
<td>MA((n_C))</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 6.1. AIC Values for AR and MA Models with Various Model Orders

Reported are population mean AIC values. Results are for patients with diabetes of study group A.
Similarly, Table 6.2 demonstrates AIC results for ARMA structure with various model orders for the patient population with diabetes of study group A. The model structure with lowest AIC value is ARMA model of order $n_A = 3$ and $n_C = 1$.

Table 6.2. AIC Values for ARMA($n_A, n_C$) Model with Various Model Orders

<table>
<thead>
<tr>
<th>$n_C$-Order</th>
<th>$n_A$-Order</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>2.9137</td>
<td>2.8862</td>
<td>2.8655</td>
<td>2.8751</td>
<td>2.8757</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>2.9086</td>
<td>2.8933</td>
<td>2.8714</td>
<td>2.8740</td>
<td>2.8757</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>2.9102</td>
<td>2.8991</td>
<td>2.8696</td>
<td>2.8767</td>
<td>2.8690</td>
</tr>
</tbody>
</table>

Reported are population mean AIC values. Results are for patients with diabetes of study group A.

Both the AR(3) and the ARMA(3,1) models are chosen for further investigation of their prediction performances. Figure 6.1 demonstrates the predicted glucose values by these models for the representative subjects of study group A. Plotted are the patient’s raw CGM data and the 2-steps-ahead (i.e., 10 min) predicted glucose values with AR(3) and ARMA(3,1) models. Table 6.3 presents the time-invariant model parameters of AR(3) and ARMA(3,1) used for the patients represented in Figure 6.1. Reported are also prediction error metrics, the sum of squares of glucose prediction error ($SSGPE$) and the relative absolute deviation ($RAD$) defined in (4.41) and (4.40), respectively.

6.3.2 Prediction Horizon (PH). Prediction error metrics, $RAD$ and $SSGPE$, are highly affected by the PH or how far into the future one is trying to predict. Table 6.4 presents mean $SSGPE$ and $RAD$ values for several PH values for the populations of both study groups. For instance, PH = 3 denotes that the glucose value 3-steps-ahead (i.e., 15 min) from the current time is predicted by (4.37) using patient’s currently available history of glucose measurements. For 10-min-ahead prediction, results show
Figure 6.1. Prediction of glucose concentrations with time-invariant models for a representative (a) healthy subject, (b) glucose-intolerant subject, and (c) subject with diabetes of study group A, with PH = 2 steps.
Table 6.3. Model Parameter and Glucose Prediction Error Metrics for Patients Represented in Figure 6.1

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Model Parameters</th>
<th>Prediction Error</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$a_1$ $a_2$ $a_3$ $c_1$</td>
<td>SSGPE (%) RAD (%)</td>
</tr>
<tr>
<td>Healthy</td>
<td>AR(3) 1.294 -0.480 0.185 – 4.27 1.26 (0.27)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARMA(3,1) 2.065 -1.237 0.172 -1.01 4.21 1.21 (0.28)</td>
<td></td>
</tr>
<tr>
<td>Glucose-Intol.</td>
<td>AR(3) 1.625 -1.019 0.392 – 4.81 1.43 (0.35)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARMA(3,1) 1.241 -0.437 0.184 0.463 4.72 1.40 (0.32)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>AR(3) 1.215 -0.154 -0.061 – 4.20 1.11 (0.24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARMA(3,1) 1.844 -0.886 0.042 -0.669 4.11 1.09 (0.24)</td>
<td></td>
</tr>
</tbody>
</table>

Results are for time-invariant models. Sum of squares of glucose prediction error ($SSGPE$) and relative absolute deviation ($RAD$) values are for PH of 2-steps (one step is 5 min). Mean $RAD$ values are reported with standard deviations given in parenthesis.

around 4-5% $SSGPE$ and 1-2% $RAD$. Prediction errors increase to around 11-12% $SSGPE$ and 5-7% $RAD$ for PH = 6. Even though prediction models are developed using filtered glucose data, $SSGPE$ and $RAD$ are computed as deviation of predicted glucose values from the patient’s raw CGM device data.

For constant parameter models (i.e., time-invariant), prediction error is also affected by the likeness between data used for model development and data used for validation. Reducing the interval of data used in model development from 24 h to 12 h (i.e., from one-half to one-fourth) does not significantly alter the $SSGPE$ and $RAD$ values: e.g., for PH = 2 and ARMA(3,1), $SSGPE$ is 5.10 ± 0.97%, 4.25 ± 0.93%, and 5.20 ± 1.06%, and $RAD$ is 1.42 ± 0.15%, 1.21 ± 0.38%, and 1.47 ± 0.37% for the healthy, glucose-intolerant, and type 2 diabetes populations of Group A, respectively. Since glucose concentrations are relatively constant at night and most of the glucose variation occurs during daytime, the model from the first 12 h data is able to capture
### Table 6.4. Prediction Performances for Several PH Values Using Time-Invariant Models

<table>
<thead>
<tr>
<th>PH (step)</th>
<th>Study Group A</th>
<th></th>
<th>Study Group B</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy</td>
<td>Glucose-Intolerant</td>
<td>Diabetes</td>
<td>Healthy</td>
</tr>
<tr>
<td></td>
<td>AR(3)</td>
<td>ARMA(3,1)</td>
<td>AR(3)</td>
<td>ARMA(3,1)</td>
</tr>
<tr>
<td>1</td>
<td>0.32(0.12)</td>
<td>0.24(0.09)</td>
<td>0.43(0.16)</td>
<td>0.31(0.11)</td>
</tr>
<tr>
<td>2</td>
<td>4.43(0.72)</td>
<td>4.40(0.72)</td>
<td>4.13(1.06)</td>
<td>4.07(1.05)</td>
</tr>
<tr>
<td>3</td>
<td>6.48(1.02)</td>
<td>6.45(1.02)</td>
<td>6.16(1.47)</td>
<td>6.06(1.47)</td>
</tr>
<tr>
<td>4</td>
<td>8.21(1.24)</td>
<td>8.17(1.25)</td>
<td>7.98(1.76)</td>
<td>7.84(1.76)</td>
</tr>
<tr>
<td>5</td>
<td>9.78(1.41)</td>
<td>9.73(1.42)</td>
<td>9.67(1.98)</td>
<td>9.51(1.97)</td>
</tr>
<tr>
<td>6</td>
<td>11.24(1.55)</td>
<td>11.19(1.56)</td>
<td>11.25(2.15)</td>
<td>11.08(2.14)</td>
</tr>
</tbody>
</table>

(A) SSGPE (%)

(B) RAD (%)

Reported are population mean SSGPE and RAD values with standard deviations given in parenthesis. One step is 5 min.
the dynamics of the remaining data. However, using the first 6 h data for model development significantly increases the error terms for PH = 2 and ARMA(3,1) to 8.37 ± 0.96%, 7.28 ± 1.26%, and 8.05 ± 2.21% SSGPE and 3.38 ± 0.37%, 3.31 ± 0.70%, and 3.54 ± 0.72% RAD for healthy, glucose-intolerant, and type 2 diabetes populations, respectively.

6.3.3 Comparison with the Worst-Case Pure-Lagged Model. It is common for any type of model that often the model predictions 'lag' the raw data, showing a shadow effect (see Figure 6.1). To address this observation directly, it is interesting to calculate metrics for a worst-case model which purely lags the current glucose value n-steps into the future (i.e., zero-order-hold). Figure 6.2 presents predicted glucose values with time-invariant ARMA(3,1) model and PH = 2 steps, compared with the worst-case pure-lagged model (i.e., zero-order-hold for 2-steps). Results are demonstrated on representative subjects of study group A (as in Figure 6.1). Glucose predictions with AR(3) model are not included in Figure 6.2, since the AR(3) shows similar prediction performance to ARMA(3,1) (see Figure 6.1). Table 6.5 provides the error metrics for AR(3), ARMA(3,1) and the pure-lagged model for the representative subjects of Figure 6.2. Results reveal that with the pure-lagged model, the error in the glucose predictions is significantly increased compared to time-invariant time-series models. Increase in the mean RAD metric is around 3-fold for all the three patients. The SSGPE show around 1-3% increase, with minimum increase detected for the healthy subject.

6.4 Glucose Prediction Results with Univariate Recursive Models

Prediction performance of the proposed recursive algorithm described in Section 6.1, is evaluated in this section. Results are also compared with the time-invariant

\[1\] Results of this section have been published in [111]
Figure 6.2. Glucose estimation with time-invariant ARMA(3,1) model and pure-lagged (i.e., zero-order-hold) glucose data, for a representative (a) healthy subject, (b) glucose-intolerant subject, and (c) subject with diabetes of study group A.
Table 6.5. Error Metrics for Patients Represented in Figure 6.2

<table>
<thead>
<tr>
<th>Subject</th>
<th>Time-Invariant AR(3)</th>
<th>Time-Invariant ARMA(3,1)</th>
<th>Pure Lagged Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ssgpe (%) rad (%)</td>
<td>ssgpe (%) rad (%)</td>
<td>ssgpe (%) rad (%)</td>
</tr>
<tr>
<td>Healthy</td>
<td>4.27 1.26(0.27)</td>
<td>4.21 1.21(0.28)</td>
<td>5.01 3.25(3.44)</td>
</tr>
<tr>
<td>Gluc.-Int.</td>
<td>4.81 1.43(0.35)</td>
<td>4.72 1.40(0.32)</td>
<td>7.55 4.70(5.15)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.20 1.11(0.24)</td>
<td>4.11 1.09(0.24)</td>
<td>6.81 4.02(4.34)</td>
</tr>
</tbody>
</table>

RAD are mean values with standard deviations given in parenthesis.

models developed in Section 6.3.

One of the drawbacks of the non-recursive models developed in Section 6.3 is that, their implementation in a portable home-use device will require prior experimental data of a typical day for each subject and individualized model development. More importantly, for best performance, patients will be obliged not to deviate from their typical daily routine, and only the patients with well-controlled diabetes will benefit from the time-invariant models. However, the population with poorly-controlled diabetes is of higher concern, since they represent the actual challenges of the disease, and they are the most to benefit from new techniques for dealing with diabetes.

Glucose and insulin dynamics show great inter- and intra-subject variation. For patients with poorly-controller diabetes, this variability is even more pronounced which necessitates recursive and subject-specific modeling algorithms for predicting future glucose concentrations of such patients.

6.4.1 Model Structure. For the recursive modeling algorithm, the ARMA model type is selected over AR, since the model error information is leveraged by the ARMA model structure (i.e., $C(q^{-1})$ term in (4.4)), and it will function as a component for disturbance modeling. During recursive identification, an online filter is simultaneously utilized to smooth the noisy data and remove the sensor noise. This
facilitates the change detection and consequently enhances the prediction accuracy. A low-pass equiripple finite impulse response (FIR) filter with normalized pass-band edge frequency of 0.42 and stop-band edge frequency of 0.5 is used for this purpose.

Figure 6.3 illustrates 30 min ahead (i.e., PH = 6) predicted glucose values for representative subjects of study group B. Results are for ARMA(2,1) with $N_W = 5$ steps (i.e., 25 min) and $\lambda = 0.5$. The forgetting factor is reduced to 0.005 in case of change detection. The model is able to track and predict 30 min ahead glucose concentrations accurately with 3.03% and 6.14% SSGPE and $2.62 \pm 0.83\%$ and $3.78 \pm 1.12\%$ RAD for the representative healthy and type 2 diabetes subjects in Figure 6.3, respectively.

An ARMA model of order $n_A = 2$ and $n_C = 1$ is found to be the optimal model to represent a patient’s glucose observations from a CGM device. Increasing the $n_A$, the autoregressive term in the model, leads to more oscillatory predictions with larger overshoots that cause increase in prediction errors. For instance, the error metrics increase to 3.84% and 7.40% SSGPE, and $2.85 \pm 0.78\%$ and $4.02 \pm 1.00\%$ RAD for the healthy subject and patient with diabetes of Figure 6.3 for ARMA(3,1) and PH = 6. On the other hand, the smaller the $n_A$, the smoother the prediction profiles become, however at a cost of increase in the ‘lag’ in predicted values. Reducing the moving average part, $n_C$, leads to consistent overshoot and higher error metrics (e.g., 3.81% and 6.76% SSGPE, and $2.80 \pm 0.81\%$ and $3.87 \pm 1.09\%$ RAD with ARMA(3,0) and PH = 6, for the representative healthy and type 2 diabetes subjects, respectively), whereas increasing the $n_C$ does not significantly improve the prediction performance.

Besides the model order, other tuning parameters used by the algorithm include the window size, $N_W$, and the regular and the reduced values for the forgetting factor, $\lambda$. These parameters and the model order are kept constant and therefore do not require individualized tuning for each subject. Window size is set to 25 min (i.e.,
Figure 6.3. Prediction of glucose concentrations with the recursive algorithm for a representative (a) healthy subject, and (b) subject with diabetes of study group B.
When a change in model parameters is detected, the value of the forgetting factor is reduced to 0.005. Furthermore, initial values for the model parameters in (4.26) are set to zero. Past glucose concentrations and past residuals required for the initialization of $\varphi_{k=0}$ in (4.25) are set to the subject’s first glucose concentration reading and zero, respectively. In other words, the proposed algorithm does not require any prior experimental data or prior tuning to account for subject variability. Therefore, the algorithm is easy to be implemented for any subject using a CGM device.

A very small or a very large value of window size, $N_W$, will significantly degrade the accuracy in glucose predictions. A small $N_W$ will reflect the possible noise in the measurements or other non-persistent signals as a significant glycemic disturbance, and a large value of $N_W$ will prevent the detection of a real glycemic disturbance sooner. Considering the effect of typical glycemic disturbances (e.g., meal consumption, exercise, stress, or change in insulin sensitivity) on glucose dynamics, $N_W$ of 5 sampling steps (i.e., 25 min) is selected. It is a value that will guarantee that a persistent deviation in glucose dynamics has occurred, and still will provide enough time for corrective action if required.

Various forgetting factor values have been tested in the range of $0.1 \leq \lambda \leq 1.0$, and $\lambda = 0.5$ was found as optimum. Predicted glucose profiles become less oscillatory and more smoother as the value of the forgetting factor is increased, however at a cost of increased ‘lag’ in predictions. On the other hand, smaller $\lambda$ values lead to oscillatory profile with larger overshoots.

6.4.2 Prediction Horizon (PH). Prediction capability of the proposed recursive algorithm for model ARMA(2,1) with $N_W = 5$ (i.e., 25 min) and $\lambda = 0.5$ is evaluated in terms of $SSGPE$ and $RAD$ in Table 6.6. Means and standard deviations of the error terms, up to six time steps of PH are provided for both subject groups. Table
Table 6.6. Prediction Performances for Several PH Values Using the Recursive Algorithm *with and without* the Change Detection Strategy

<table>
<thead>
<tr>
<th>Study Group A</th>
<th>Study Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PH</strong></td>
<td><strong>Healthy</strong></td>
</tr>
<tr>
<td></td>
<td>Change Detection</td>
</tr>
<tr>
<td></td>
<td>(step)</td>
</tr>
<tr>
<td><strong>(A) SSGPE (%)</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.32(0.06)</td>
</tr>
<tr>
<td>2</td>
<td>0.91(0.18)</td>
</tr>
<tr>
<td>3</td>
<td>1.80(0.38)</td>
</tr>
<tr>
<td>4</td>
<td>2.57(0.76)</td>
</tr>
<tr>
<td>5</td>
<td>2.84(0.80)</td>
</tr>
<tr>
<td>6</td>
<td>3.02(1.05)</td>
</tr>
<tr>
<td><strong>(B) RAD (%)</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.25(0.07)</td>
</tr>
<tr>
<td>2</td>
<td>0.69(0.19)</td>
</tr>
<tr>
<td>3</td>
<td>1.32(0.33)</td>
</tr>
<tr>
<td>4</td>
<td>2.11(0.49)</td>
</tr>
<tr>
<td>5</td>
<td>2.17(0.67)</td>
</tr>
<tr>
<td>6</td>
<td>2.55(0.79)</td>
</tr>
</tbody>
</table>

Reported are population mean *SSGPE* and *RAD* values with standard deviations given in parenthesis. One step is 5 min.
6.6 also includes results for the recursive algorithm \textit{without} the change detection strategy. This means that Steps 3 and 4 of the algorithm described at Section 6.1 are not included in the computations.

Comparing results of Table 6.6 for \textit{with} and \textit{without} change detection, reveals significantly smaller \textit{SSGPE} and \textit{RAD} values for the \textit{with} case. The superiority of the proposed algorithm \textit{with} change detection is even more pronounced for higher PH values. This shows the efficiency of the change detection component and the superior predictive capability of the proposed algorithm. Similarly, comparison of prediction error metrics of the time-invariant models in Table 6.4 and the recursive algorithm in Table 6.6 shows that the time-invariant models lead to significantly larger error terms, as they are not able to adapt to the physiological changes in a subject’s metabolism or response to large glycemic disturbances such as meal or exercise.

\textbf{6.4.3 Continuous Glucose Error Grid Analysis (CG-EGA).} Accuracy of the predictions is also evaluated using CG-EGA method described in Section 4.7.2. Table 6.7 demonstrates the CG-EGA error matrix for 30 min ahead glucose predictions using the proposed recursive algorithm with the change detection. There were no observations in the hyperglycemic range for the healthy population; therefore Table 6.7(A) does not include columns for hyperglycemia. In the hypoglycemic range, 92.31\%, 7.69\%, and 0\% of the predicted data result in accurate predictions, benign errors, and erroneous predictions for the healthy population and 92.94\%, 5.29\%, and 1.77\% for the population with diabetes. These values are 91.50\%, 7.87\%, and 0.63\% during normoglycemia and 89.79\%, 8.70\%, and 1.51\% during hyperglycemia for the population with diabetes. In contrast, for the healthy population, 95.47\%, 4.53\%, and 0\% of the data predicted by the algorithm are considered as accurate, benign errors, and erroneous predictions during normoglycemia, respectively.

\textbf{6.4.4 Variation in Model Parameters.} The initial values for model parameters,
Table 6.7. Error Matrix of CG-EGA for Predicted Glucose Values with $PH = 6$ for Study Group B

(A) Healthy Group (There is no data in hyperglycemic range for this group)

Point Error Grid Zones

<table>
<thead>
<tr>
<th>Hypoglycemia</th>
<th>Normoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>$BG \leq 70$ mg/dl</td>
<td>$70 &lt; BG \leq 180$ mg/dl</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rate Error Grid Zones</th>
<th>A</th>
<th>D</th>
<th>E</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>92.31%</td>
<td>0%</td>
<td>0%</td>
<td>85.17%</td>
<td>0.46%</td>
<td>0%</td>
</tr>
<tr>
<td>B</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>9.52%</td>
<td>0.32%</td>
<td>0%</td>
</tr>
<tr>
<td>uC</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>1.74%</td>
<td>0.23%</td>
<td>0%</td>
</tr>
<tr>
<td>IC</td>
<td>7.69%</td>
<td>0%</td>
<td>0%</td>
<td>2.29%</td>
<td>0.27%</td>
<td>0%</td>
</tr>
<tr>
<td>uD</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>lD</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>uE</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>lE</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

(B) Diabetes Group

Point Error Grid Zones

<table>
<thead>
<tr>
<th>Hypoglycemia</th>
<th>Normoglycemia</th>
<th>Hyperglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>$BG \leq 70$ mg/dl</td>
<td>$70 &lt; BG \leq 180$ mg/dl</td>
<td>$BG &gt; 180$ mg/dl</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rate Error Grid Zones</th>
<th>A</th>
<th>D</th>
<th>E</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>81.76%</td>
<td>1.18%</td>
<td>0%</td>
<td>72.43%</td>
<td>1.18%</td>
<td>0%</td>
<td>70.23%</td>
<td>1.00%</td>
<td>0%</td>
<td>0.88%</td>
<td>0%</td>
</tr>
<tr>
<td>B</td>
<td>11.18%</td>
<td>0.59%</td>
<td>0%</td>
<td>17.05%</td>
<td>0.84%</td>
<td>0.04%</td>
<td>18.23%</td>
<td>0.33%</td>
<td>0.17%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>uC</td>
<td>2.35%</td>
<td>0%</td>
<td>0%</td>
<td>3.49%</td>
<td>0.30%</td>
<td>0%</td>
<td>4.16%</td>
<td>0.25%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>IC</td>
<td>2.94%</td>
<td>0%</td>
<td>0%</td>
<td>3.58%</td>
<td>0.25%</td>
<td>0%</td>
<td>4.01%</td>
<td>0.17%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>uD</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0.04%</td>
<td>0%</td>
<td>0%</td>
<td>0.17%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>lD</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0.04%</td>
<td>0.17%</td>
<td>0%</td>
<td>0.08%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>uE</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0.21%</td>
<td>0%</td>
<td>0%</td>
<td>0.42%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>lE</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0.30%</td>
<td>0.08%</td>
<td>0%</td>
<td>0.59%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Accurate Predictions | Benign Errors | Erroneous Predictions
\(\hat{\theta}_{i,0}\) in (4.26), are assumed zero and with the recursive identification they are expected to converge to subject-specific values through time. Therefore, initialization of the algorithm does not require any prior glucose concentration data or model identification. Figures 6.4 and 6.5 display the adaptation of the model parameters to daily life changes for the representative subjects of study group B. Model parameters converge to good parameter values rapidly, and reliable glucose predictions are made in less than 2 h after starting the recursive algorithm. This period can be reduced further for a specific patient who uses this method routinely, by assigning \(\hat{\theta}_{i,k=0}\) to the parameter values from an earlier prediction series. However, this will limit the algorithm’s implementation on an ambulatory portable device. Variation of the model parameters in Figures 6.4 and 6.5 illustrates the effectiveness of the change detection strategy and the adaptability of the algorithm developed to changes in glucose excursions.

6.4.5 Comparison with the Worst-Case Pure-Lagged Model. Figure 6.6 demonstrates 30 min ahead glucose predictions with the proposed recursive algorithm (i.e., including the change detection strategy) compared with the worst-case pure-lagged model (i.e., zero-order-hold for 6-steps). Results are demonstrated on representative subjects of study group B. Prediction error metrics for the two methods are provided in Table 6.8. The error in the glucose predictions decrease around 2.5 to 3-fold for SSGPE and 2.5 to 3.5-fold for RAD with the proposed algorithm compared to worst-case pure-lagged model for PH = 6.

<table>
<thead>
<tr>
<th>Rep. Subject</th>
<th>Recursive Alg. with Change Detection</th>
<th>Pure Lagged Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SSGPE (%)</td>
<td>mean RAD (%)</td>
</tr>
<tr>
<td>Healthy</td>
<td>3.03</td>
<td>2.62(0.83)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6.14</td>
<td>3.78(1.12)</td>
</tr>
</tbody>
</table>

Standard deviations are given in parenthesis.
Figure 6.4. Variation in model parameters (i.e, $\hat{a}_1$, $\hat{a}_2$ and $\hat{c}_1$ for the ARMA(2,1) model) for a representative healthy subject of study group B. Predicted glucose concentrations are for PH=6 steps (i.e., 30 min). The representative subject is the same as in Figure 6.3(a).
Figure 6.5. Variation in model parameters (i.e., \( \hat{a}_1 \), \( \hat{a}_2 \) and \( \hat{c}_1 \) for the ARMA(2,1) model) for a representative subject with diabetes of study group B. Predicted glucose concentrations are for PH=6 steps (i.e., 30 min). The Representative subject is the same as in Figure 6.3(b).
Figure 6.6. Glucose estimation with the proposed recursive algorithm and pure-lagged (zero-order-hold) glucose data, for a representative (a) healthy subject, and (b) subject with diabetes of study group B.
6.5 Conclusions

The performance of the univariate subject-specific glucose prediction algorithm developed has been evaluated in this chapter. The proposed recursive algorithm can dynamically adapt to inter-/intra-subject variability, since models are derived from a patient’s own CGM data and are recursively updated at each sampling step to include the most recent glucose dynamics. Integrating the recursive modeling strategy with a change detection method is shown to significantly enhance the prediction performance, as the effect of glycemic disturbances are more rapidly captured and model convergence is sped up.

Results show that prediction errors are significantly reduced with recursive identification of the models, and predictions are further improved with the change detection component. CG-EGA analyses demonstrate accurate predictions of 90% or more with the algorithm developed.

The proposed recursive algorithm uses a low-order linear time-series model, ARMA(2,1), which requires identification of only three model parameters at each sampling step. Additionally, it does not require any tailoring or prior experimental data before implementation. Therefore, it is a good candidate for installation in a portable home-use device. Predicted glucose values can be used for early hypoglycemic/hyperglycemic alarms and for closing the glucose regulation loop with an insulin pump.

Furthermore, the proposed algorithm does not require any prior announcement or information about glycemic disturbances such as meal size and time. It is able to effectively detect and adapt to any variation in glucose dynamics. Results show that good glucose predictions are possible by using recent CGM history only. On the other hand, incorporating inputs such as insulin amount delivered, meal size,
or exercise intensity may improve the model’s glucose prediction accuracy, however additional inputs will increase the number of parameters to be identified and therefore increase the computational burden. It will also mean extra load in terms of subject intervention, since a subject will be required to enter detailed meal or exercise related information.

Glucose regulation in the body is a complex and a nonlinear process. Linear models would be less accurate compared to nonlinear models for describing variations of a nonlinear system in a wide range of conditions. However, frequent sampling and recursive model identification interfaced with a change detection method compensates for their simplicity. The proposed algorithm is designed to dynamically adapt to inter-and intra-subject variability and to provide satisfactory prediction performance in the presence of any glycemic disturbances.

One possible limitation of the proposed algorithm is that compared to the nonlinear compartmental glucose models available in the literature, the proposed model may not provide insight about physiological consequences of glycemic perturbations such as glucose production/removal rate and glucose transport within tissues. However, the linear subject-specific modeling algorithm developed in this thesis is able to represent any glycemic variation, even for the patients with poorly-controlled diabetes, which is mostly unachievable with the physiological models.

The algorithm assumes availability of a reliable CGM device that provides accurate glucose measurements. CGM sensors are not yet widely adopted among patients with diabetes, and their main use is currently limited to clinical studies. Therefore, widespread real life implementation of the algorithm developed currently may be limited. However, development of reliable CGM technologies is an extensively on-going research, and current limitations with such devices will most probably be solved in the near future.
CHAPTER 7

CLOSED-LOOP GLUCOSE CONTROL WITH UNIVARIATE MODELS - RESULTS

The long-term complications of diabetes (e.g., diabetic ketoacidosis, kidney failure, and cardiovascular diseases) can be reduced by controlling the blood glucose concentrations within normoglycemic limits. Current therapy with insulin injections or a manual pump restricts patients to follow a rigid lifestyle, and it may lead to prolonged hyperglycemia or hypoglycemia, since it is difficult for the patient to decide on the optimal insulin amount/rate and correct timing of injection/infusion with changing daily life conditions (e.g., diet, exercise, stress or illness). Therefore, closing the glucose control loop with a fully automated insulin pump will revolutionize management of blood glucose concentrations for people with diabetes and significantly improve the lives of the patients.

The second part of this thesis focuses on the development of a closed-loop control algorithm for fully automated blood glucose regulation with exogenous insulin administration. The individual components of the algorithm are described in Chapter 5, and its high-level block diagram is provided in Figure 5.1. A low-pass filter is used to estimate a patient’s current blood glucose concentration (i.e., controlled variable) from the subcutaneous glucose measurement of a CGM device. Depending on the current blood glucose estimate, a desired future glucose trajectory is determined. The recent history of estimated blood glucose concentrations and past insulin infusion rates are used to develop a linear model that describes glucose-insulin interactions in the patient’s body, and whose parameters are recursively updated at each sampling step to include the most recent glucose dynamics. This model is used to predict the patient’s future glucose excursion. The subject-specific model is then integrated to a model-based control strategy to calculate the required insulin infusion rate that will bring patient’s glucose concentrations to desired levels.
The proposed model-based control algorithm utilizes the univariate glucose prediction models developed and evaluated in Chapter 4 and Chapter 6, respectively. Under closed-loop conditions, recent history of past insulin infusion rates (i.e., input signal) is also included to the univariate time-series models to form the ARIMAX structure defined by (5.4). Two well-known model-based control methods, the generalized predictive control (GPC) and the linear quadratic control (LQC), are used for computations of the required insulin rates that will keep a patient’s blood glucose concentrations within the desired normoglycemic range. The control algorithm developed also includes two time-delay compensators; (i) a lag-filter to account for the time-delay between measured subcutaneous glucose and controlled blood glucose concentrations (see Section 5.2.1), and (ii) a Smith predictor type structure that considers the delay in insulin action due to its slow subcutaneous absorption (see Section 5.2.2).

The performance of the proposed control algorithm is demonstrated on two simulated patient populations for two case scenarios that include simultaneous meal and physiological disturbances. The objective is to keep blood glucose concentrations within tight control with postprandial levels below 160 mg/dl and normalization of glucose levels back to fasting range (120-70 mg/dl) within 2-3.5 h after a meal challenge [10].

7.1 Algorithm Overview

The proposed control algorithm that utilizes the GPC strategy is described step-by-step as follows:

- **Step 0:** Decide on the model order (i.e., $n_A$, $n_B$, $n_C$ and $d$) for the ARIMAX model in (5.4). Assign the values of the design parameters $N_y$, $N_u$, $Q$, $R$, $u_{min}$, $u_{max}$, $\Delta_{max}$ in (5.17), and the initial values for $\varphi_1$, $\hat{\theta}_0$ in (5.5) and (5.6), respec-
tively. Also, assign the value of $\tau = 1/a$ in (5.2) and compute the $P = P^n/P^d$ polynomial in (5.14).

- **Step 1:** Read the glucose measurement from the CGM device.

- **Step 2:** For the model structure defined in Step 0, identify the ARIMAX model parameters ($\hat{\theta}_k$) using the weighted RLS and change detection methods described in Section 4.4 and Section 4.5, respectively.

- **Step 3:** Estimate the current blood glucose concentration using (5.14). And predict its future excursion using (5.9) and (5.16).

- **Step 4:** Using the strategy discussed in Section 5.5 and depicted in Figure 5.3, determine the reference glucose trajectory, $\psi_{ref,k+j}$ in (5.17), that depends on the estimated current blood glucose value calculated at Step 3.

- **Step 5:** Using the variables calculated at Steps 3 and 4, solve the constrained quadratic optimization problem of (5.17), to obtain the vector of future insulin infusion rates, $[\Delta u_k \ldots \Delta u_{k+N_u-1}]$.

- **Step 6:** Administer only the first insulin infusion rate, $u_k = \Delta u_k + u_{k-1}$ from Step 5 to the patient.

- **Step 7:** Update the $\varphi_{k+1}$ in (5.5) to include the new CGM measurement from Step 1, and update the $\hat{\theta}_k$ in (5.6) with its new value from Step 2. Then, return to Step 1.

The proposed control algorithm that utilizes the LQC strategy is described step-by-step as follows:

- **Step 0:** Decide on the model order (i.e., $n_A$, $n_B$, $n_C$ and $d$) for ARIMAX model in (5.4). Assign the values of the design parameters $Q$ and $R$ in (5.18), and the
initial values for $\varphi_1, \hat{\theta}_0$ in (5.5) and (5.6), respectively. Also, assign the value of $\tau = 1/a$ in (5.2) and compute the $P = P^n/P^d$ polynomial in (5.14).

- **Step 1:** Read the glucose measurement from the CGM device.

- **Step 2:** For the model structure defined in Step 0, identify the ARIMAX model parameters ($\hat{\theta}_k$) using the weighted RLS and change detection methods described in Section 4.4 and Section 4.5, respectively.

- **Step 3:** Estimate the current blood glucose concentration using (5.23), and identify the $G, H,$ and $F$ matrices in (5.25) by state space realization of (5.23).

- **Step 4:** Using the $G$ and $H$ matrices from Step 3, estimate the future states using (5.27), and calculate the feedback gain $K$ using (5.21) and (5.22).

- **Step 5:** Using the variables calculated at Steps 4, determine the insulin infusion rate given by (5.26), and administer it to the patient.

- **Step 6:** Update the $\varphi_{k+1}$ in (5.5) to include the new CGM measurement from Step 1, and update the $\hat{\theta}_k$ in (5.6) with its new value from Step 2. Then, return to Step 1.

### 7.2 Simulated Subject Data

Two virtual patient simulators for type 1 diabetes are used to evaluate the control algorithms developed: one utilizes the models of GlucoSim [86] and the other utilizes the models developed by Hovorka et al. [6], [33]. Both simulators describe glucose-insulin interactions in the body with physiological compartmental models. Model equations and model parameters of both simulators are provided in Appendix B.

It is assumes that a virtual subject’s glucose concentration is monitored with a reliable CGM device that provides glucose readings at 5 min intervals, a typical
value for CGM devices currently available in the market. The peripheral glucose concentration of the GlucoSim model described in (B.4) is assumed to depict a patient’s subcutaneously measured glucose value by a CGM sensor, while the plasma glucose concentration of Hovorka in (B.36) is delayed for 5 min to depict such sensor signal. Additionally, to depict sensor noise of a real CGM device, Gaussian noise with standard deviation of 2.5 mg/dl is added to the data from both GlucoSim and Hovorka models.

With changing daily life conditions, patients with diabetes generally experience glycemic disturbances which affect their blood glucose excursions and insulin requirements. Such disturbances mostly occur simultaneously and sometimes unexpectedly. In this thesis, glycemic disturbances are categorized into two groups: (i) external disturbances such as meal consumption or exercise whose effects and onset are predictable, and (ii) the unpredictable physiological disturbances such as metabolic changes caused by stress, illness, or variations in a patient’s insulin sensitivity/resistance. Glucose variations due to physiological changes are more random in nature compared to external glycemic disturbances. Most of the time, patients may not be aware of the onset of such physiological perturbations, and therefore, deciding on corrective insulin regimen during such conditions may not be easy for the patients.

For the simulation studies used to evaluate the proposed closed-loop algorithms, meal consumption and change in the insulin sensitivity are selected to depict the external and the physiological glycemic disturbances, respectively. Insulin sensitivity describes the effect of plasma insulin on net glucose disappearance (i.e., stimulation of peripheral glucose uptake and inhibition of hepatic glucose production) in the body. In this thesis, changes in insulin sensitivity are generated with variation of the rate constants of insulin-dependent glucose uptake, term $k$ in (B.9), and liver glucose production, term $a_1$ in (B.19), of the GlucoSim model. Similarly,
the three insulin sensitivity indexes of the Hovorka model (i.e., $S_{IT}$, $S_{ID}$, and $S_{IE}$ in Table B.4) are varied from their reported nominal values to simulate a patient with changing insulin resistance. For both simulators, the patient population is created by varying the insulin sensitivity parameters by 10% increments in the range of -70% to +30% of their nominal values (i.e., total of 11 possible moves). An asymmetric range is selected, so that the populations will represent more of an ‘unstable’ (i.e., insulin resistant) patient group. Including the case of no-change in insulin sensitivity, a population with total of 121 patients, each experiencing a different insulin sensitivity change scenario is simulated with both models.

**Case Scenario A:** Glycemic disturbances are depicted with three equal-size meal challenges of 50 g carbohydrate (CHO) content, consumed at 30 min, 16 h and 32 h after closing the loop with a simultaneous change in a patient’s insulin sensitivity at 26 h.

**Case Scenario B:** A more realistic 2-day scenario that includes 8 standard-size meals and simultaneous changes in the diet and insulin sensitivity is also simulated. The two-day scenario includes predefined meal content and timing on day 1, and both 50% increased CHO intake and one hour late lunch on day 2. Meal schedule for day 1 is: Breakfast at 8:30 AM with 30 g of CHO consumption, lunch at 12:00 PM with 40 g of CHO, snack at 4:00 PM with 15 g of CHO, and dinner at 7:30 PM with 50 g of CHO. The insulin sensitivity change is assumed to occur at 4:00 AM during the second day.

### 7.3 Model Structure

The ARIMAX model in (5.4) with constant model order (i.e., $n_A$, $n_B$, $n_C$ and $d$ constant) is selected, and the model parameters in (5.6) are identified at each sampling step. The model order is selected based on pharmacokinetic profiles following
subcutaneous injections of rapid-acting insulin. Action curves of subcutaneously administered rapid-acting insulin show onset within 5-15 min, peak in 45-90 min and overall duration about 3-4 h (see Table 1.1). Assuming that insulin will have its most dominant effect on glucose regulation until its peak time, $n_B = 12$ (i.e., input action with duration of 60 min) is selected and 15 min delay in insulin action (i.e., $d = 3$) is assumed. Additionally, $n_A = 2$, $n_C = 1$ is used and the initial model parameters in (5.6) are set to zero except $\tilde{b}_{0,k=0}$ which is set to 1.

Selection of model order and initial parameters can be individualized for each patient using system identification techniques and prior open-loop CGM and insulin data from the patient. However, this will limit the implementation of the control algorithm on an ambulatory home-use device. Therefore, in this thesis, such prior tuning or tailoring steps are skipped and the time period (or transition period) required for the system to tune itself and the cost of such periods is investigated.

### 7.4 Design Parameters

Forgetting factor of 0.5 is used and its value is reduced to 0.005 in case of a change detection. Other design parameters include the weight on input and output terms in the quadratic cost functions of GPC and LQC, $\varrho$ and $\varpi$ in (5.17) or $Q$ and $R$ in (5.18). Several $\varrho/\varpi$ ratios were investigated and a ratio of 5 is selected. In addition to the exponential reference trajectory described in Section 5.5), the effort on trajectory tracking during hypoglycemia is increased by increasing the $\varrho/\varpi$ ratio by 3-fold for glucose concentrations below 80 mg/dl. Prediction horizons for control input and output of GPC, $N_u$ and $N_y$ in (5.17), are set to 15 and 20, respectively.

A constant time-delay between subcutaneous and blood glucose concentrations, $\tau$ in (5.2), is assumed. $\tau$ values of 4-10 min [112] and values less than 5 min [113] have been reported. More recently, [114] reported $\tau$ values of $7.1 \pm 5.5$ min.
and $2.2 \pm 6.2 \, \text{min}$ for two commercial subcutaneous CGM sensors. Comparing blood and peripheral glucose excursions of GlucoSim, a time-constant around 4-5 min is identified for the system which is consistent with the values reported in the literature. Similarly, the blood glucose values of Hovorka model are delayed by 5 min to represent subcutaneous measurements.

7.5 Closed-Loop Results for Case Scenario A

The feasibility of the algorithm developed is examined for the most delayed route (i.e., subcutaneous glucose measurement and subcutaneous insulin delivery), and therefore the most difficult case for the blood glucose control problem. Blood glucose regulation with the proposed GPC algorithm and $\tau = 5$ is demonstrated in Figure 7.1. Case Scenario A described in Section 7.2 which consists of three equal-size meal disturbances is considered. The patient is assumed to have regular insulin sensitivity at the beginning and experience 70% (i.e., the worst case) reduction in insulin sensitivity at 26 h after closing the loop. Demonstrated results are for a virtual subject simulated by the GlucoSim model. Closed-loop results with overestimated $\tau$ values (i.e., 10 min and 20 min) are also included in Figure 7.1. For the same case scenario, blood glucose regulation with the LQC algorithm are presented in Figure 7.2.

The transition period which is defined as the time elapsed until the system tunes itself, is clearly detected in insulin infusion rate plots in Figures 7.1 and 7.2. The transition period is around 4 h for both GPC and LQC. Control action is aggressive and rapidly changing at the start, since we start with an un-tuned model or far away from true glucose dynamics, and gradually smooths as more data become available to capture the patient’s true glucose dynamics. The GPC demonstrates less

---

$^1$Results of this section have been published in [115]
Figure 7.1. Closed-loop glucose regulation with GPC in response to Case Scenario A (Section 7.2) with 70% insulin reduction. Results are for a virtual subject simulated with GlucoSim model, (a) blood glucose concentration for $\tau = 5, 10$ and 20 min, and (b)-(d) subcutaneous insulin infusion for $\tau = 5, 10$ and 20 min, respectively.
Figure 7.2. Closed-loop glucose regulation with LQC in response to Case Scenario A (Section 7.2) with 70% insulin reduction. Results are for a virtual subject simulated with GlucoSim model, (a) blood glucose concentration for $\tau = 5, 10$ and 20 min, and (b)-(d) subcutaneous insulin infusion for $\tau = 5, 10$ and 20 min, respectively.
aggressive control action during this period compared to the LQC. For $\tau = 5 \text{ min}$, neither control strategy causes severe hypoglycemia (i.e., glucose concentration below 50 mg/dl) during the transition period, since the constraint on $\Delta u_k$ in (5.11) prevents excessive insulin administration.

The effective response of the proposed GPC and LQC algorithms to external glycemic disturbances is observed with the rapid insulin action taken at meal times (16 h and 32 h, excluding the first meal consumed during the transition period) as shown in Figures 7.1 and 7.2, respectively. Both algorithms are also able to detect and provide a fast response to physiological variations. Rapid insulin action is observed in Figures 7.1 and 7.2 at 26 h, when insulin sensitivity is reduced and much higher fasting insulin infusion rates are required. Results demonstrate that both closed-loop strategies are able to keep blood glucose concentrations within the desired limits even for the most insulin resistant subject of the patient population of GlucoSim.

For the GPC algorithm with $\tau = 5$, the patient in Figure 7.1 achieves postprandial glucose peaks at 154.2 mg/dl and 156.2 mg/dl after the meals at 16 h and 32 h, respectively. Corresponding postprandial maximums with the LQC algorithm are 157.2 mg/dl and 164.6 mg/dl in Figure 7.2. During the last meal challenge at 32 h, with the 70% reduction in insulin sensitivity, the LQC leads to a postprandial peak slightly over the desired value of 160 mg/dl. However, neither strategy leads to hyperglycemia or hypoglycemia (blood glucose concentrations above 180 mg/dl or below 50 mg/dl respectively) after the initial 4 h transition period. Even in presence of insulin resistance, both algorithms are able to settle to the desired fasting glucose level (i.e., 80 mg/dl). The glucose peaks following the first meal in Figures 7.1 and 7.2 would have been much lower, if the simulations were started with initial model parameter values tuned for the subject in priori. The lower values of the postprandial peaks for the meals at 16 h and 32 h illustrate this case.
Various statistics evaluating the mean population performance of the GPC and the LQC glucose control algorithms developed are presented in Table 7.1. Since glucose regulation during the initial transition period will not provide true performance statistics, control performance is evaluated for the 16-48 h time period.

In Table 7.1 reported are population mean values with the standard deviations given in parentheses for the population simulated with GlucoSim. Compared to GPC, LQC results in more sluggish control action depicted with smaller values for the area under the curve (AUC) of insulin, and consequently higher mean and maximum glucose concentrations. Neither control strategy causes hypoglycemic or hyperglycemic episodes (i.e., number of Subject\text{BG}<50 and Subject\text{BG}>180 is 0). With the GPC algorithm and \( \tau = 5 \) min, 21 patients out of the 121 patient population of GlucoSim experience slight hypoglycemia (i.e., Subject\text{60−50.BG}), with all the cases recovered within 10 min. Under same conditions, the LQC strategy does not lead to any cases of slight hypoglycemia. The feasibility of the proposed closed-loop strategies is further demonstrated as both algorithms are able to bring blood glucose levels back to 100 mg/dl within 2-2.5 h following a meal (i.e., \( t_{100BG} \)).

Table 7.1 also provides performance statistics for the overestimated \( \tau \) values, 10 and 20 min. For some systems, the true time-delay (\( \tau \) value) between the subcutaneous and blood glucose levels may not be attainable, and one may only have a rough estimate for its value. The statistics reported in Table 7.1 and the glucose concentration plots of Figures 7.1 and 7.2 reveal that for \( \tau = 10 \) min, which is closer to true system dynamics (i.e., 5 min), both algorithms are still able to provide satisfactory blood glucose regulation. However, glucose regulation starts to deteriorate for \( \tau = 20 \) min as the \( \tau \) estimate diverges from its true value.

The closed-loop performance is also evaluated in terms of deviations from the desired reference trajectory. Table 7.1 reports the mean population values for sum
<table>
<thead>
<tr>
<th></th>
<th>GlucoSim Model</th>
<th>Hovorka Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GPC</td>
<td>LQC</td>
</tr>
<tr>
<td></td>
<td>$\tau = 5$</td>
<td>$\tau = 10$</td>
</tr>
<tr>
<td>$G_{\text{mean}}$ (mg/dl)</td>
<td>89.20(4.39)</td>
<td>90.59(5.20)</td>
</tr>
<tr>
<td>$G_{\text{max}}$ (mg/dl)</td>
<td>152.69(6.21)</td>
<td>158.73(5.93)</td>
</tr>
<tr>
<td>$G_{\text{min}}$ (mg/dl)</td>
<td>64.22(5.77)</td>
<td>63.56(5.24)</td>
</tr>
<tr>
<td>$G_{\text{settle}}$ (mg/dl)</td>
<td>80.57(1.04)</td>
<td>80.94(1.24)</td>
</tr>
<tr>
<td>$t_{100\text{BG}}$ (min)</td>
<td>116.05(8.27)</td>
<td>118.24(8.93)</td>
</tr>
<tr>
<td>$AUC_{\text{ins}} \times 10^2$ (mU)</td>
<td>354.83(58.5)</td>
<td>367.33(53.83)</td>
</tr>
<tr>
<td>$SSD$ (%)</td>
<td>2.37(0.62)</td>
<td>2.50(0.46)</td>
</tr>
<tr>
<td>$Subject_{60-50,BG}$</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>$Subject_{BG&lt;50}$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$Subject_{160-180,BG}$</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>$Subject_{BG&gt;180}$</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

All the values are population means with standard deviations given in parenthesis, and are calculated for the 16–48 h time period of the Case Scenario A (Section 7.2) that includes 2-meals.

$G_{\text{mean}}$, $G_{\text{max}}$, and $G_{\text{min}}$ are the mean, worst maximum, and worst minimum blood glucose values within the time period. $G_{\text{settle}}$ is the post-meal settling blood glucose concentration. $t_{100\text{BG}}$ is the time elapsed for glucose levels to come back to 100 mg/dl after a meal consumption. $AUC_{\text{ins}}$ is the total area under the curve for insulin infusion. $SSD$ is the sum of squared deviations.

$Subject_{60-50,BG}$, $Subject_{BG<50}$, $Subject_{160-180,BG}$ and $Subject_{BG>180}$ stand for number of subjects that experience at least one occasion of blood glucose levels in the range of 60-50 mg/dl, below 50 mg/dl, in range of 160-180 mg/dl and above 180 mg/dl, respectively for minimum of 10 min time period.
of squared deviations (SSD). SSD is defined similar to the prediction error metric, $SSGPE$ given by (4.41). For SSD computations, (4.41) is modified such that $y$ represents the current desired glucose value (which depends on previous-step glucose measurement), and $\hat{y}$ represents the actual achieved glucose concentration at the current sampling step. By definition, (4.41) also penalizes the difference between desired and actual glucose even when the achieved glucose level is better than the desired. Therefore, a conditional strategy is applied: for glucose levels below $80 \text{ mg/dl}$, deviations are included only if $(y_k - \hat{y}_k) \geq 0$, and for glucose levels above $80 \text{ mg/dl}$, only $(y_k - \hat{y}_k) \leq 0$ are included. Results in Table 7.1 show that, glucose regulation with LQC leads to higher deviation terms (SSD) compared to GPC, as expected from the more sluggish control actions in Figure 7.2 compared to Figure 7.1.

Validity of the reported results are also evaluated using a second patient population that is simulated with Hovorka model described in Appendix B.2. Figures 7.3 and 7.4 demonstrate glucose regulation using the proposed GPC and LQC algorithms, respectively, for a representative patient simulated with the Hovorka model. Results are for $\tau = 5 \text{ min}$ and the three equal-size meal challenge with simultaneous 70% reduction in a patient’s insulin sensitivity. For comparison, results for the representative patient of GlucoSim under same conditions (Figures 7.1 and 7.2 for $\tau = 5 \text{ min}$) are also included in the plots. The Hovorka patient show similar results to GlucoSim patient, with postprandial glucose peaks at 155.2 $\text{ mg/dl}$ and 158.7 $\text{ mg/dl}$ after the meals at 16 $\text{ h}$ and 32 $\text{ h}$ with the GPC algorithm, and 157 $\text{ mg/dl}$ and 167.4 $\text{ mg/dl}$ with the LQC. Population mean statistics for the population of Hovorka are included in Table 7.1.

7.6 Closed-Loop Results for Case Scenario B

$^1$Results of this section have been published in [115]
Figure 7.3. Closed-loop glucose regulation with GPC in response to Case Scenario A (Section 7.2) with 70% insulin reduction. Results are for $\tau = 5$ min and a virtual subject simulated with Hovorka and GlucoSim models, (a) blood glucose concentration, and (b)-(c) subcutaneous insulin infusion for GlucoSim and Hovorka models, respectively.
Figure 7.4. Closed-loop glucose regulation with LQC in response to Case Scenario A (Section 7.2) with 70% insulin reduction. Results are for $\tau = 5 \text{ min}$ and a virtual subject simulated with Hovorka and GlucoSim models, (a) blood glucose concentration, and (b)-(c) subcutaneous insulin infusion for GlucoSim and Hovorka models, respectively.
The performance of the closed-loop algorithm developed is also tested for the Case Scenario B described in Section 7.2. The glycemic disturbances consists of 2-day multiple meal challenge with changes in the diet and reduction in insulin sensitivity during the second day. Figures 7.5 and 7.6 provide blood glucose regulation results with both control strategies (i.e., GPC and LQC) applied on representative virtual subjects of GlucoSim and Hovorka, respectively. Initial transition periods are not included in the plots, since they display similar characteristics as in Figures 7.1-7.4 (i.e., transition period of 4 h).

Postprandial glucose peaks slightly over the desired 160 mg/dl are observed with both LQC (GlucoSim 166.18 mg/dl, Hovorka 167.16 mg/dl) and GPC (GlucoSim 162.84 mg/dl, Hovorka 164.01 mg/dl) during the second day after lunch when the meal challenge is increased by 50% and the patient also experiences the worst insulin sensitivity change (i.e., 70% reduction). GPC demonstrates faster adaptability (rapid insulin rise coinciding with meal timings), and therefore, more active control actions which result in lower postprandial peaks and faster normalization of blood glucose concentrations after meals.

Table 7.2 provides population mean performance statistics for the 2-day multiple meal challenge. LQC results in more sluggish control action compared to GPC with smaller $AUC_{ins}$, higher mean and maximum glucose concentrations ($G_{mean}$ and $G_{max}$), and higher deviation terms ($SSD$) for both populations of GlucoSim and Hovorka. LQC does not lead to any hypoglycemic or hyperglycemic episodes, or slight hypoglycemia (i.e., $Subject_{BG<50} = Subject_{50-50,BG} = Subject_{BG>180} = 0$). However, it leads to significantly increased number of patients that experience slight hyperglycemia compared to GPC. This number is 64 and 58 compared to 20 and 25 for the populations of GlucoSim and Hovorka, respectively. None of the virtual patients experience hypoglycemic or hyperglycemic episodes with the GPC algorithm,
Figure 7.5. Closed-loop glucose regulation with GPC and LQC in response to Case Scenario B (Section 7.2) with 70% insulin reduction. Results are for $\tau = 5\text{ min}$ and a virtual subject simulated with GlucoSim model, (a) blood glucose concentration, and (b)-(c) subcutaneous insulin infusion with GPC and LQC, respectively.
Figure 7.6. Closed-loop glucose regulation with GPC and LQC in response to Case Scenario B (Section 7.2) with 70% insulin reduction. Results are for $\tau = 5$ min and a virtual subject simulated with Hovorka model, (a) blood glucose concentration, and (b)-(c) subcutaneous insulin infusion with GPC and LQC, respectively.
while 13 and 14 patients out of the 121 patient populations of GlucoSim and Hovorka, respectively, experience slight hypoglycemia. Both control algorithms provide satisfactory glucose control performance by bringing the postprandial glucose levels back to normoglycemic limits within the desired 2-3.5 \( h \) time period and avoiding any severe hypoglycemia or hyperglycemia.

Table 7.2. Closed-Loop Performance for Case Scenario B

<table>
<thead>
<tr>
<th></th>
<th>GPC</th>
<th>LQC</th>
</tr>
</thead>
<tbody>
<tr>
<td>( G_{mean} ) (mg/dl)</td>
<td>95.75(6.94)</td>
<td>96.72(6.82)</td>
</tr>
<tr>
<td>( G_{max} ) (mg/dl)</td>
<td>155.84(8.13)</td>
<td>157.44(7.02)</td>
</tr>
<tr>
<td>( G_{min} ) (mg/dl)</td>
<td>68.57(8.64)</td>
<td>68.80(8.46)</td>
</tr>
<tr>
<td>( AUC_{ins} \times 10^2 ) (mU)</td>
<td>747.55(90.36)</td>
<td>860.57(95.13)</td>
</tr>
<tr>
<td>( SSD ) (%)</td>
<td>2.42(0.54)</td>
<td>2.64(0.51)</td>
</tr>
<tr>
<td>Subject(_{60−50,BG})</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Subject(_{BG&lt;50})</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subject(_{160−180,BG})</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Subject(_{BG&gt;180})</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The variables in the first column have the same definitions as in Table 7.1. All values are population means with standard deviations given in parenthesis, and are calculated for the overall 50 \( h \) time period of Case Scenario B (Section 7.2). Results are for \( \tau = 5 \) min.

7.7 Conclusions

An adaptive model-based control algorithm has been developed for fully automated blood glucose regulation. The adaptability of the controller is provided with recursive subject-specific glucose prediction models developed in Chapter 4. Variations in glucose-insulin dynamics due to external and physiological glycemic disturbances are tracked by online identification of the model. At each sampling step, model parameters are updated to include a patient’s most recent glucose-insulin dynamics information and the patient’s future glucose excursion is estimated. The identified
subject-specific model is then integrated with the model-based control algorithms developed for calculating the appropriate control action (i.e., insulin infusion rate). The optimal insulin infusion rate is determined by solving an optimization problem that minimizes the deviation of predicted glucose values from a desired reference glucose trajectory.

In the literature, many of the proposed glucose control algorithms assume the minimally delayed intravenous site for either glucose sensing or insulin delivery, or both (see Sections 3.2 and 3.3). Differently, we focus on the route with the longest delay (i.e., subcutaneous) for both glucose sensing and insulin administration. Two delay compensators are introduced to the control algorithm, in order to account for the time-lag between subcutaneous and blood glucose concentrations and delays in insulin action due to its slow absorption from the subcutaneous tissue. While developed by keeping in mind the challenges with subcutaneous glucose-insulin route, explicitly expressed time-delay compensators makes the application of the proposed algorithms straightforward to any other glucose-insulin route (i.e., it requires the adjustment of the time-delay values only).

The performance of the controller has been tested with GPC and LQC methods to provide effective blood glucose regulation in response to multiple meal challenges with simultaneous challenge on a subject’s insulin sensitivity. Results have been evaluated on two virtual populations with type 1 diabetes that are simulated using the models of GlucoSim and Hovorka. The closed-loop algorithm developed has been shown to keep blood glucose concentrations within the desired normoglycemic limits avoiding hyperglycemia and hypoglycemia, even for the most challenging subcutaneous-glucose and subcutaneous-insulin route, and for a population with poorly controlled diabetes (i.e., insulin resistant).

Predictive control methods have been successfully used in the industry for
systems with large time-delays. Its predictive structure provides a powerful tool not only to deal with time-delays in the system, but also to estimate the effect of future control and manipulated variables. These estimates are then used in a feedback loop for calculating the optimal input signal that will bring the system to the desired state. Prediction into the future allows corrective action to be taken much sooner compared to classical feedback control in response to disturbances (e.g., avoiding administration of excessive insulin that might cause postprandial hypoglycemia). Constraint handling and penalizing the input actions (which will avoid high and aggressive insulin actions) are other favorable aspects of the model-based predictive control methods. The only drawback of the model-based control systems is that the controller performance is strongly dependent on the accuracy of the model used to represent the true dynamics of the system. In this thesis, this problem is addressed by avoiding the use of physiological glucose-insulin models which are mostly representative of an average patient and are hard to tune for subject-specific needs. Instead, a subject-specific modeling algorithm which is recursively updated at each sampling time to dynamically capture a subject’s glucose variation is developed and used by the proposed closed-loop blood glucose regulation algorithm.

Another advantage of the proposed algorithm is that it is designed to dynamically respond and reject different types of glycemic disturbances (e.g., external and physiological). The algorithm does not require any prior disturbance announcements or information. Furthermore, it does not utilize any physiological representation of glucose-insulin dynamics, additional disturbance models, or manual inputs provided by the patient. The closed-loop algorithm is designed to function in a fully automated manner and does not require any patient specific tailoring or prior experimental data before implementation.
CHAPTER 8
GLUCOSE PREDICTION WITH MULTIVARIATE MODELS - RESULTS

A subject’s daily glucose excursions and glucose metabolism are affected by food intake, physical activity, emotional stimuli and lifestyle. Especially, physical activity and stress are known to have a significant effect on the whole-body fuel metabolism, and consequently on glucose-insulin dynamics. However, the number of studies focusing on modeling the glucose homeostasis during exercise and stress is limited to [116], [55], [56], and [57] as discussed in Section 3.1.4.

The third part of this thesis focuses on the development of a reliable multivariate subject-specific modeling algorithm for predicting a subject’s future glucose concentrations. The univariate time-series models that are evaluated in Chapter 6 and that utilize a subject’s recent glucose concentration history are extended to include additional information on the subject’s physical and emotional condition. Physiological measurements from a multi-sensor body monitor (BodyMedia SenseWear Pro3, Pittsburgh, PA) are used for this purpose. Such physiological signals supplement the CGM information and improve the prediction accuracy of the glucose predicting models.

Time-series methods are utilized to analyze the discrete time data from the CGM and armband sensors, and to develop empirical subject-specific linear models. A subject’s own glucose sensor and armband data are used for model development. Measurements at a high frequency (e.g., 5 min sampling time) provide more insight not only into the subject’s glucose profile during the day, but also into the rate at which glucose variations occur and the effect of physiological signals on these variations. Frequently measured physiological data enables obtaining more reliable data-driven or empirical models for predicting a subject’s future glucose concentrations.
The mathematical components of the multivariate algorithm developed are discussed in Chapter 4. Using CGM and armband data, multivariate time-series analyses are utilized to develop a VARMAX model structure defined in (4.14) and (4.16). The model parameters are recursively identified at each sampling step to include the information from new measurements. The weighted RLS algorithm described in Section 4.4 is used for this purpose. In addition, the parameter change detection strategy described in Section 4.5 is implemented for improved performance and data tracking, and faster adaptation in presence of disturbances.

The multivariate algorithm developed does not require any training data or manual inputs that will demand frequent patient intervention. It is assumed that both the CGM and the armband data are wirelessly acquired by the algorithm. The models developed are subject-specific, since they are developed from a patient’s own frequently measured data, and are updated at each sampling step to portray any variation in the patient’s glucose metabolism.

The prediction performance of the proposed multivariate algorithm is evaluated on data collected from subjects with type 2 diabetes under free living conditions. A real life application of the algorithm is also demonstrated for early (i.e., 30 min in advance) hypoglycemic alarms.

8.1 Algorithm Overview

Multiple variables observed simultaneously with a CGM sensor and an armband are used to form a subject-specific multivariate time-series model. A patient’s future glucose concentration (i.e., 1-output variable) is predicted using past and current physiological measurements from the armband (i.e., $m$-input variables) and past CGM sensor measurements. For the $m$-input 1-output case, the VARMAX model described in (4.14) and (4.16) is expressed as:
where $y_k$ is the CGM glucose measurement at the $k$th sampling step. The physiological signals from the armband form the model input variables $\{u_{1,k}, \ldots, u_{m,k}\}$, and $\epsilon_k$ denotes the noise term. At the $k$th sampling instant, the model parameters are expressed with $\{a_{1,k}, \ldots, a_{n_{A,k}}\}$, $\{c_{1,k}, \ldots, c_{n_{C,k}}\}$ and $b_{j,k}^{(i)}$ where $i = 1, \ldots, m$ and $j = 0, \ldots, n_{B}^{(i)}$. $m$ denotes the total number of inputs and $n_{B}^{(i)}$ is the model order of the $i$th input. $d^{(i)}$ introduces $d$-steps of delay to the $i$th input that accounts for the possible delay in input action.

Equation (8.1) can be rewritten in the following linear regression form:

$$y_k = \varphi_k^T \hat{\theta}_{k-1} + \epsilon_k = \hat{y}_k + \epsilon_k$$

(8.2)

where $y_k$ and $\hat{y}_k$ represent the actual glucose measurement and its model estimated value at the $k$th sampling instant, respectively. $\epsilon_k$ denotes the residual terms caused by the difference between a patient’s glucose dynamics and its model. $\varphi_k$ denotes the vector of historical CGM and armband measurements and $\hat{\theta}_{k-1}$ is the estimate of time-varying model parameters. For the multivariate VARMAX model in (8.1), $\varphi_k$ and $\hat{\theta}_{k-1}$ are expressed as:
The weighted recursive least squares (RLS) and the change detection methods described in Sections 4.4 and 4.5, respectively, are used to identify the model parameters, $\hat{\theta}_k$, at the $k$th sampling step. Then, with known parameter values, the VARMAX model in (8.1) is appended $n$-steps into the future to predict the patient’s future glucose concentrations, $\hat{y}_{k+n|k}$. For the multivariate model, the last term in the $n$-steps-ahead predictor described in (4.38) requires future values of the exogenous input variables, $\{u^{(i)}_{k+j}\}$, which are unknown until new measurements become available from the armband.

In this thesis, it is assumed that the $m$-input variables from the armband follow a VARMA($n_A,n_C$) model. This model is then used to predict future values of the $m$-armband signals. Without loss of generality, the model orders $n_A$ and $n_C$ of the following VARMA are assumed to be equal to the orders in (8.1):

$$U_k = \sum_{i=1}^{n_A} A_{i,k} U_{k-i} + \sum_{i=1}^{n_C} C_{i,k} \epsilon_{k-i} + \epsilon_k$$  \hspace{1cm} (8.5)

In (8.5), $U_k = [u^{(1)}_k \ldots u^{(m)}_k]^T$ and $\epsilon_k = [\epsilon^{(1)}_k \ldots \epsilon^{(m)}_k]^T$ are the system output and noise vectors of length $m$, respectively. $A_{i,k}$ and $C_{i,k}$ are $m \times m$ matrices composed of model parameters at the $k$th sampling step:
The proposed multivariate glucose prediction algorithm is described step-by-step as follows:

- **Step 0:** Decide on the model order (i.e., $n_A$, $n_C$, $n_B^{(i)}$ and $d^{(i)}$) for the VARMAX model in (8.1). Assign the initial values for $\varphi_1$ in (8.3) and $\hat{\theta}_0$ in (8.4).

- **Step 1:** Read the glucose measurement from the CGM device and the physiological signals from the armband.

- **Step 2:** For the model structure defined at Step 0, identify the model parameters ($\hat{\theta}_k$) using the weighted RLS method in (4.28)-(4.30).

- **Step 3:** Check for change detection using (4.31). If a change is detected, assign a flag and go to Step 4. Otherwise go to Step 5. (Flags are stored for $N_W$ sampling instants).

- **Step 4:** Check if flag was assigned for all of the last $N_W$ steps. If the answer is yes, at the next sampling step, reduce the value of the forgetting factor for one step and replace $\hat{\theta}_N$ in (4.31) with its new estimate. Otherwise, keep the normal values of $\lambda$ and $\hat{\theta}_N$.

- **Step 5:** Calculate the $n$-steps-ahead predicted armband signals using the VARMA model in (8.5) and (8.6), and the weighted RLS method described in Section 4.4.
- **Step 6:** Using the predicted armband values from Step 5, calculate the $n$-steps-ahead predicted glucose value using (4.38), (4.35) and (4.39).

- **Step 7:** Update $\varphi_{k+1}$ in (8.3) to include the new measurements from Step 1, and update $\hat{\theta}_k$ in (8.4) with its new value from Step 2. Then, return to Step 1.

### 8.2 Subject Data

Data used in this study consists of glucose concentration and physiological signals collected from 5 subjects with type 2 diabetes under free living conditions ($23.8 \pm 2.4$ days of data per subject). A Medtronic MiniMed Continuous Glucose Monitor, MMT-7012 (Medtronic MiniMed, Northridge, CA) was used to gather the glucose data. This device measures subcutaneous glucose concentrations every five minutes. The body monitoring system SenseWear Pro3 (BodyMedia Inc., Pittsburgh, PA) was used for collection of metabolic, physical activity and lifestyle information. It provides seven signals to describe a subject’s activity and emotional conditions: energy expenditure (EE), average longitudinal acceleration (LA), transverse acceleration peaks (TAP), transverse acceleration mean of absolute difference (TAM), near-body temperature (BT), heat flux (HF) and galvanic skin response (GSR). The SenseWear monitor provides measurements every minute, therefore, the physiological data were trimmed to include the data points at the same time instants as those from the glucose monitor.

### 8.3 SenseWear Pro3 Armband

The body monitoring system SenseWear Pro3 provides metabolic, physical activity and lifestyle information. The armband weights 80 g and is worn on the upper right arm as shown in Figure 8.1 without obstructing daily activities. It continuously monitors and records physical activity and lifestyle related physiological signals in free living conditions for up to 2 weeks.
Figure 8.1. SenseWear Pro3 Armband by BobyMedia Inc. [4]

The device consists of four sensors: (1) a heat-flux sensor that determines the rate at which heat is dissipating from the body by the measurement of heat loss between the skin and a vent on the side of the armband, (2) a temperature sensor that measures the surface temperature of the skin, (3) a galvanic skin response sensor that measures skin impedance which varies due to sweating and emotional stimuli reflected by water content of the skin and the constriction or dilation of the vascular periphery, and (4) a two-axis accelerometer which tracks movement and body position and measures motion activity. The sensors provide measurements for EE, LA, BT, HF, GSR, TAP and TAM every minute. The SenseWear Pro3 also accurately assesses physiological information such as number of steps taken, duration and level (METs) of physical activity, sleep duration and efficiency, quality of life behavior and stress levels [117].

8.4 Model Structure

Model structure is selected based on preliminary analyses performed on models with constant parameters. Using the data from the CGM device and the SenseWear armband described in Section 8.2, various VARMAX models of different structures (i.e., different input variable combinations) and different orders (i.e., $n_A$, $n_C$, $n_B^{(i)}$ and $d^{(i)}$ in (8.1)) are developed and examined for each patient individually; by using
MATLAB System Identification Toolbox. The Akaike information criterion (AIC) described in Section 4.3 is utilized for best model selection. The AIC value of each model is calculated using (4.22) over the entire data of a patient, and the model with the lowest AIC value is selected.

For the multivariate VARMAX model in (8.1), \( n_A = 2 \) and \( n_C = 1 \) provide the best model (i.e., lowest AIC value) regardless of the various input combinations used. Among the 7 signals from the armband, TAP and TAM are found to have insignificant contribution on a patient's glucose excursions. The remaining 5 signals, \( U_k = [EE_k, LA_k, HF_k, GSR_k, BT_k]^T \), are used to construct 5-input 1-output VARMAX models of different orders with \( n_B = [1, 1, 2, 2, 2] \) and \( d = [4, 4, 5, 7, 5] \) providing the best model based on the AIC criterion.

Besides the model order, other tuning parameters used by the algorithm include the window size, \( N_W \), and the regular and the reduced values for the forgetting factor, \( \lambda \). These parameters and the model order are kept constant and therefore do not require tailoring for each subject. Window size is set to 25 min (i.e., \( N_W = 5 \) steps), and \( \lambda = 0.5 \) is used. When a change in model parameters is detected the value of \( \lambda \) is reduced to 0.005. Furthermore, past glucose and physiological measurements required for the initialization of \( \varphi_{k=0} \) in (8.3) are set to patient’s first measurements from the CGM sensor and armband, respectively. And the past residual terms in (8.3) are set to zero. The initial model parameters, \( \hat{\theta}_{k=0} \) in (8.4), are assigned to zero except \( \left\{ \hat{b}_{0,k=0}^{(1)}, \ldots, \hat{b}_{0,k=0}^{(m)} \right\} \) which are set to 1.

8.5 Prediction Performance \(^1\)

Prediction performance of the multivariate subject-specific models developed are evaluated on the subject data described in Section 8.2. For each subject, the data

\(^1\)Results of this section have been published in [118]
is divided into separate segments that start at 3AM each day and last for 24 hours. This process leads to total of 97 data sets. With a specified model structure and order from Section 8.4, the proposed multivariable glucose prediction algorithm is then evaluated on the 97 data sets individually. The algorithm starts with an un-tuned model (i.e., $\hat{\theta}_{k=0} = 0$, except $\{\hat{b}_{0,k=0}^{(1)}, \ldots, \hat{b}_{0,k=0}^{(m)}\}$ which are set to 1) for each data set.

Figure 8.2 illustrates a typical data set for one of the subjects. The proposed algorithm is implemented with $n_A = 2$, $n_C = 1$, $n_B = [1, 1, 2, 2, 2]$, $d = [4, 4, 5, 7, 5]$, $NW = 5$ steps, $\lambda = 0.5$ and $\hat{\theta}_0 = 0$, and without any patient specific tailoring. In Figure 8.2 demonstrated are the raw CGM data and the 30 min ahead predicted glucose values with the multivariate algorithm. For comparison, the 30 min ahead predicted glucose values with the univariate algorithm summarized in Section 6.1 are also included.

![Figure 8.2. Glucose prediction with the multivariate and the univariate algorithms.](image)

Figure 8.2 demonstrates that it takes longer for the multivariate model to tune to true patient dynamics (observed with the oscillations in the first hours), since
it requires identification and convergence of a larger number of model parameters (i.e., 11 versus 3) compared to the univariate algorithm. However, after the initial tuning period, glucose predictions with the multivariate model follow the CGM sensor measurements very closely, while the glucose values predicted by the univariate model show large deviations from the sensor data.

Figures 8.3-8.7 demonstrate the SenseWear armband signals used for the development of the multivariate glucose predictions demonstrated in Figure 8.2. Number of model parameters used to describe each individual input signal is given by \( n_B^{(i)} \), and the delay term, \( d^{(i)} \), describes the time-steps elapsed till the effect of a specific signal becomes detectable on the glucose excursions.

![Energy expenditure signal from the SenseWear armband used for the multivariate glucose predictions in Figure 8.2.](image)

**Figure 8.3.** Energy expenditure signal from the SenseWear armband used for the multivariate glucose predictions in Figure 8.2.
Figure 8.4. Average longitudinal acceleration signal from the SenseWear armband used for the multivariate glucose predictions in Figure 8.2.

Figure 8.5. Heat flux signal from the SenseWear armband used for the multivariate glucose predictions in Figure 8.2.
Figure 8.6. Galvanic skin response signal from the SenseWear armband used for the multivariate glucose predictions in Figure 8.2.

Figure 8.7. Near-body temperature signal from the SenseWear armband used for the multivariate glucose predictions in Figure 8.2.
Table 8.1 presents the prediction performance of the proposed algorithm over the entire 97 data sets. Prediction performance is numerically evaluated using two error metrics that describe the deviation of the $n$-steps-ahead predicted glucose values from the actual observed CGM data; (i) the relative absolute deviation ($\text{RAD}$) defined in (4.40), and (ii) the sum of squares of glucose prediction error ($\text{SSGPE}$) defined in (4.41). The mean $\text{RAD}$ and $\text{SSGPE}$ values are reported for both the multivariate and the univariate algorithms. Results are for 30 min ahead prediction (i.e., $n = 6$ steps) with $N_W = 5$ steps (i.e., 25 min) and $\lambda = 0.5$. The forgetting factor is reduced to 0.005 in case of change detection. Results in Table 8.1 demonstrate that prediction accuracy is improved and error metrics are decreased with the multivariate algorithm compared to the univariate algorithm.

<table>
<thead>
<tr>
<th></th>
<th>Univariate Alg.</th>
<th>Multivariate Alg.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RAD (%)</strong></td>
<td>5.77 (7.18)</td>
<td>4.24 (5.14)</td>
</tr>
<tr>
<td><strong>SSGPE (%)</strong></td>
<td>8.81</td>
<td>7.43</td>
</tr>
</tbody>
</table>

For SSGPE reported are the mean values. For RAD reported are the mean values with standard deviations given in parentheses.

### 8.6 Early Hypoglycemia Detection

In this section, the multivariate models developed are implemented to provide *early* hypoglycemic alarms. The algorithm is evaluated prospectively on the patient data described in Section 8.2. Avoiding hypoglycemia while keeping glucose within the narrow normoglycemic range of 70-120 mg/dl is a major challenge for patients with diabetes. For instance, many patients experience nocturnal hypoglycemia. Glucose concentrations below 40 mg/dl cause severe impairment in the nervous system that have the potential to lead to seizure, diabetic coma and eventually death.

Some of the CGM sensors available in the market provide a hypoglycemic alarm when the measured glucose decreases below a user specified threshold. However,
patients will benefit more from an *early* alarm that predicts the hypoglycemic episode before it occurs, providing time for corrective action to be taken. A few of the commercially available CGM sensors provide such *early* alarms by linear extrapolation of the rate of change of glucose concentrations into the future, [119], [120], and [121]. In contrast, the algorithm developed in this thesis uses reliable subject-specific models that utilize both CGM data and physiological signals from an armband to predict future glucose concentrations and provide *early* alarms.

The multivariate glucose prediction algorithm is used to predict future hypoglycemic episodes before they occur. When the $n$-steps-ahead predicted glucose level is below a threshold value assigned for hypoglycemia (e.g., $60 \text{ mg/dl}$), an alarm is triggered at that sampling instant, $k$. The alarm signifies that the patient will experience a hypoglycemia $n$-steps-ahead from the current time, $k + n$. The alarm issued is considered false positive if the patient’s actual CGM glucose measurement at time step $k + n$ is above the predefined threshold, and true positive if it is below the threshold value. False negative occurs when an alarm is not issued at the $k$th step (i.e., hypoglycemia not predicted), but the patient’s glucose at step $k + n$ is actually below the threshold value.

Hypoglycemia threshold of $60 \text{ mg/dl}$ and $n = 6$ steps (i.e., 30 min) is selected to evaluate the performance of the proposed *early* alarm algorithm. Out of the total 34330 glucose measurements from the patients described in Section 8.2, only 194 are below or equal to $60 \text{ mg/dl}$. Rate of hypoglycemia is low, since subjects have type 2 diabetes and therefore have an active glucagon response to reduce the chance of hypoglycemia. Of the 34330 decisions performed by the algorithm, 34071 are true negative (i.e., alarm not-issued correctly), 144 are true positive (i.e., alarm issued correctly), 50 are false negative (i.e., missed alarm), and 65 are false positive (i.e., false alarm). Sensitivity to detect *early* hypoglycemia which is expressed in (8.7) and
defined as probability of true positive alarms among all hypoglycemic events occurred is 74%. And the false positive rate (i.e., type I error) defined in (8.8) is 0.2%.

\[
Sensitivity(\%) = \frac{TruePositives}{TruePositives + FalseNegatives} \times 100 \tag{8.7}
\]

\[
FalseAlarmRate(\%) = \frac{FalsePositives}{FalsePositives + TrueNegatives} \times 100 \tag{8.8}
\]

Figure 8.8 demonstrates a portion of the data when one of the subjects experiences hypoglycemia. Shown are the actual CGM sensors measurements and 30 min ahead predicted glucose values with the proposed multivariate alarm algorithm for 60 mg/dl threshold. The red-shaded area in the figure represents the period of early alarms that predicts an incidence of hypoglycemia within the next 30 min. The patient experiences two nocturnal hypoglycemic episodes for which the algorithm correctly alarms 30 min before their occurrences with each alarm lasting for 20 min.

Figure 8.8. Early hypoglycemic alarms with the multivariate algorithm for 30 min ahead prediction and 60 mg/dl hypoglycemia threshold.
Figure 8.9. ROC curves for prediction horizons of 15, 30 and 45 min (i.e., \(PH = 3, 6, \text{ and } 9\) steps). Hypoglycemia thresholds are increased at 10 mg/dl intervals in the range of 60-120 mg/dl.

Figure 8.9 demonstrates the receiver operating characteristic (ROC) curves for 15, 30 and 45 min ahead predictions. The markers on the each ROC curve correspond to different thresholds that increase at 10 mg/dl intervals in the range of 60-120 mg/dl. Figure 8.9 shows that the threshold value selected for hypoglycemia has a significant effect on alarm performance, with the lowest sensitivity observed at 60 mg/dl threshold and the highest sensitivity observed at 120 mg/dl. Increasing the threshold improves the sensitivity of the alarms to detect hypoglycemia, but at a cost of decreased specificity, a measure used to correctly identify the absence of hypoglycemic events. Another parameter that affects the alarm performance is
the prediction horizon \((PH)\). Figure 8.9 demonstrates that sensitivity can also be improved by reducing the \(PH\). The highest sensitivity is observed for 15 min ahead prediction (i.e., \(PH = 3\) steps) regardless of the threshold selected. However, \(PH\) should extend long enough to ensure time for the necessary corrective action (e.g., food ingestion) to avoid hypoglycemia.

8.7 Conclusions

The univariate modeling algorithm for predicting glucose concentrations that is developed and evaluated in Chapter 4 and Chapter 6, respectively, is extended to a multivariate model that uses not only a subject’s glucose measurements from a CGM device, but also several physiological signals depicting the subject’s physical activity and emotional conditions that are known to have a significant effect on the glucose metabolism. Physiological signals are collected with a multi-sensor body monitor worn on the arm. At each sampling step (e.g., 5 min), the measurements from the glucose sensor and the body monitor are wirelessly transmitted to the proposed algorithm which then computes the future glucose concentrations of the subject. Such predicted glucose values can be used for insulin dose adjustments and hypoglycemia/hyperglycemia prevention.

Time-series approach is employed for the development of the multivariate linear models. The models consist of total of 11 parameters that are recursively identified using weighted RLS at each sampling step. A variable forgetting factor is implemented with a change detection strategy which achieves good data tracking not only during slow frequency changes in glucose dynamics but also during drastic and sudden variations.

Prediction performance analyses demonstrate that error metrics \(RAD\) and \(SSGPE\) are significantly reduced with the additional measurements from the arm-
band (i.e., multivariate algorithm), when compared to predictions done solely on glucose measurements (i.e., univariate algorithm). Results show $5.77 \pm 7.18\%$ RAD and $8.81\%$ SSGPE for the univariate algorithm, when predicting 30 min into the future. These error metrics are reduced to $4.24 \pm 5.14\%$ RAD and $7.43\%$ SSGPE for the multivariate algorithm which supports the fact that the physiological signals have a significant effect on glucose metabolism.

The algorithm is also successfully implemented to provide early hypoglycemic alarms. The proposed multivariate algorithm provides 30 min ahead predicted glucose values that closely follow the sensor data (Figure 8.8), which improves the alarm performance (i.e., sensitivity). Results show that sensitivity to detect hypoglycemia is 74% with false positive rate of 0.2%, for $PH$ of 30 min and 60 mg/dl hypoglycemia threshold. The sensitivity can further be improved by reducing the $PH$. However, it should be long enough to provide time for corrective action (e.g., food ingestion). 30 min is a relatively large $PH$. Increasing the hypoglycemia threshold will also improve the sensitivity. However, it will lead to increased number of false alarms (Figure 8.9), which might frustrate patients and make them ignore the alarms.

The multivariate modeling algorithm developed is subject-specific and dynamically captures inter-/intra-subject variability. It does not require any prior experimental data, tuning for each subject, or disturbance announcements. Therefore, it can easily be implemented for any subject using a CGM sensor and a multi-sensor body monitor.
CHAPTER 9
CLOSED-LOOP GLUCOSE CONTROL WITH MULTIVARIATE MODELS - RESULTS

Physical activity and emotional stimuli such as stress are known to have a significant effect on a subject’s whole-body fuel metabolism. Closing the blood glucose regulation loop with a fully automated system that also takes into account the effect of exercise on insulin requirements will significantly improve the lives of the patients with diabetes. Currently, patients have to manually adjust their insulin intake for anticipated physical activities.

The last part of this thesis focuses on the development of a closed-loop algorithm for fully automated blood glucose regulation that utilizes physiological measurements from a multi-sensor body monitor in addition to the glucose measurements from a continuous glucose monitoring (CGM) device. Real-time measurements from an armband that provide information on a patient’s physical and emotional condition are shown to have a significant effect on the patient’s glucose excursions in Chapter 8.

The individual components of the multivariate algorithm developed are discussed in Chapter 5 and its high-level block diagram is depicted in Figure 9.1. A patient wears a CGM device and an armband that measure the patient’s subcutaneous glucose concentration and several physiological signals, respectively, in discrete intervals through time. The lag-filter developed in Section 5.2.1 is used to estimate the patient’s current blood glucose concentration (i.e., controlled variable) from the CGM device measurement. Depending on the current blood glucose estimate, a desired future glucose trajectory is determined as described in Section 5.5. The recent history of estimated blood glucose concentrations, past insulin infusion rates and past measurements from the armband are used to develop a multivariate linear model whose
parameters are updated at each sampling step. This model is then used to predict the patient’s future glucose excursions and is integrated to a model-based control strategy that calculates the required insulin infusion rate to bring the patient’s glucose concentrations to the desired levels.

![Block diagram of the proposed multivariate closed-loop strategy.](image)

The proposed multivariate closed-loop algorithm utilizes the multivariate glucose prediction models developed and evaluated in Chapter 4 and Chapter 8, respectively. Under closed-loop conditions, recent history of past insulin infusion rates (i.e., manipulated variable) is also included to the multivariate time-series model of (8.1) to form the VARIMAX structure defined in (9.1), where the physiological signals from the arm band are considered as the measurable disturbance variables. The generalized predictive control (GPC) algorithm described in Section 5.4.1 is then used to compute the required insulin infusion rates that will keep blood glucose concentrations within the desired normoglycemic range. The multivariate control algorithm developed also includes two time-delay compensators discussed in Sections 5.2.1 and 5.2.2; (i) a lag-filter that accounts for the time-delay between the measured subcutaneous
glucose and the controlled blood glucose concentrations, and (ii) a Smith predictor type structure that considers the delay in insulin action due to its slow subcutaneous absorption.

The performance of the proposed algorithm is tested with two clinical closed-loop experiments performed on a patient with type 1 diabetes (age 21 years, body mass index, BMI 23.1 kg/m²) during a meal and physical activity challenge. The closed-loop algorithm acquired patient’s CGM and armband data every 10 min and accordingly calculated the required basal insulin infusion rate. Insulin was administered in a fully automated manner without any food or activity announcements (e.g., no information on meal/exercise size or time). Physiological measurements were wirelessly transmitted from the armband; thus, the effect of physical activity was captured without requiring any patient intervention.

9.1 Algorithm Overview

Under closed-loop conditions, the effect of insulin delivered is also included in the multivariate time-series developed in Chapter 8. For the multivariate case, the ARIMAX model given in (5.4) and used in the univariate GPC control algorithm becomes a VARIMAX model that can be expressed as:

\[ A_k(q^{-1}) \Delta y_k = q^{-d} B_k(q^{-1}) \Delta u_{k-1} + q^{-d^{(1)}} H_k^{(1)}(q^{-1}) \Delta \varphi_{k-1}^{(1)} + \ldots + q^{-d^{(i)}} H_k^{(i)}(q^{-1}) \Delta \varphi_{k-1}^{(i)} + \ldots + q^{-d^{(m)}} H_k^{(m)}(q^{-1}) \Delta \varphi_{k-1}^{(m)} + C_k(q^{-1}) \epsilon_k \]  

(9.1)

In (9.1), \( \Delta y_k = y_k - y_{k-1} \) and \( y_k \) represents the process output (i.e., glucose
concentration measured by a CGM device) at the \( k \)th sampling step. \( u_k \) is the manipulated variable (i.e., insulin infusion rate) and \( \{ \vartheta_k^{(1)} \ldots \vartheta_k^{(m)} \} \) are the measurable disturbances (i.e., \( m \) signals from the armband) at the \( k \)th sampling step, and the \( \epsilon_k \) denotes the noise term. The time-varying polynomials \( A_k(q^{-1}) \), \( B_k(q^{-1}) \), \( C_k(q^{-1}) \) and \( H_k^{(i)}(q^{-1}) \) are defined as:

\[
A_k(q^{-1}) = 1 - a_{1,k} q^{-1} - \ldots - a_{n_A,k} q^{-n_A}
\]

(9.2)

\[
B_k(q^{-1}) = b_{0,k} + b_{1,k} q^{-1} + \ldots + b_{n_B,k} q^{-n_B}
\]

(9.3)

\[
C_k(q^{-1}) = 1 + c_{1,k} q^{-1} + \ldots + c_{n_C,k} q^{-n_C}
\]

(9.4)

\[
H_k^{(i)}(q^{-1}) = h_{0,i,k}^{(i)} + h_{1,i,k}^{(i)} q^{-1} + \ldots + h_{n_{\vartheta}^{(i)},k}^{(i)} q^{-n_{\vartheta}^{(i)}}
\]

(9.5)

In (9.2)-(9.5), \( q^{-1} \) is the back-shift operator. The \( \{a_{1,k} \ldots a_{n_A,k}\} \), \( \{b_{0,k} \ldots b_{n_B,k}\} \), \( \{c_{1,k} \ldots c_{n_C,k}\} \) and \( \{h_{0,i,k}^{(i)} \ldots h_{n_{\vartheta}^{(i)},k}^{(i)}\} \) are the time-varying model parameters of the controlled, manipulated, noise, and the \( i \)th disturbance variables with their model orders defined by \( n_A \), \( n_B \), \( n_C \) and \( n_{\vartheta}^{(i)} \), respectively.

Equation (9.1) can be rewritten in the following linear regression form:

\[
y_k = \varphi_k^T \theta_{k-1} + \epsilon_k = \hat{y}_k + e_k
\]

(9.6)

where \( y_k \) and \( \hat{y}_k \) represent the actual glucose measurement and its model estimated value at the \( k \)th sampling instant, respectively. \( e_k \) denotes the residual terms caused by the difference between a subject’s glucose dynamics and its model. \( \varphi_k \) denotes the vector of historical CGM and armband measurements, and insulin delivery rates, whereas \( \hat{\theta}_{k-1} \) is the estimate of time-varying model parameters. For the multivariate VARIMAX model in (9.1), \( \varphi_k \) and \( \hat{\theta}_{k-1} \) are expressed as:
\[
\varphi_k = \begin{bmatrix} 
\Delta y_{k-1} & \Delta y_{k-n_A} & \Delta u_{k-d-1} & \Delta u_{k-d-n_B} & \ldots \\
\Delta \vartheta^{(i)}_{k-d(i)-1} & \ldots & \Delta \vartheta^{(i)}_{k-d(i)-n(i)} & e_{k-1} & \ldots & e_{k-n_C} 
\end{bmatrix}^T
\] (9.7)

\[
\hat{\theta}_{k-1} = \begin{bmatrix} 
\hat{a}_{1,k-1} & \hat{a}_{n_A,k-1} & \hat{a}_{n_A,k-1} & \hat{b}_{0,k-1} & \ldots & \hat{b}_{n_B,k-1} & \ldots \\
\hat{h}^{(i)}_{0,k-1} & \ldots & \hat{h}^{(i)}_{n(i),k-1} & \hat{c}_{1,k-1} & \ldots & \hat{c}_{n_C,k-1} 
\end{bmatrix}^T
\] (9.8)

The weighted recursive least squares (RLS) and the change detection methods described in Sections 4.4 and 4.5, respectively, are used to identify the model parameters, \( \hat{\theta}_k \), at the \( k \)th sampling step. Then, with known parameter values, the VARIMAX model in (9.1) is used in a model-based control algorithm to compute the required insulin infusion rate. More specifically, the GPC algorithm described in Section 5.4.1 is used for closing the blood glucose regulation loop.

The cost function of GPC defined in (5.7) requires \( n \)-steps-ahead predicted glucose values, \( \hat{y}_{k+n|k;\hat{\theta}_k} \). For the multivariate VARIMAX model in (9.1), the \( n \)-steps-ahead predictor is expressed as:

\[
\hat{y}_{k+n|k;\hat{\theta}_k} = G_n(q^{-1}) \Delta u_{k+n-1} + \Gamma_n(q^{-1}) \Delta u_{k-1} + F_n(q^{-1}) y_k^f + L_n^{(1)}(q^{-1}) \Delta \vartheta^{(1)}_{k+n-1} + \ldots + L_n^{(m)}(q^{-1}) \Delta \vartheta^{(m)}_{k+n-1} + \Lambda_n^{(1)}(q^{-1}) \Delta \vartheta^{(1)}_{k-1} + \ldots + \Lambda_n^{(m)}(q^{-1}) \Delta \vartheta^{(m)}_{k-1}
\] (9.9)

In (9.9), \( \Delta u_k^f = (1/C)\Delta u_k, y_k^f = (1/C)y_k \) and \( \Delta \vartheta^{(i)}_k = (1/C)\Delta \vartheta^{(i)}_k \), and the polynomials \( E_n, \Gamma_n, G_n, L_n^{(i)} \) and \( \Lambda_n^{(i)} \) are found after solving for the following
Diophantine equations:

\[ C_k(q^{-1}) = E_n(q^{-1}) A_k(q^{-1}) \Delta + q^{-n} F_n(q^{-1}) \]  \hspace{1cm} (9.10) 

\[ E_n(q^{-1}) B_k(q^{-1}) = G_n(q^{-1}) C_k(q^{-1}) + q^{-n} \Gamma_n(q^{-1}) \]  \hspace{1cm} (9.11) 

\[ E_n(q^{-1}) H_k^{(i)}(q^{-1}) = L_n^{(i)}(q^{-1}) C_k(q^{-1}) + q^{-n} \Lambda_n^{(i)}(q^{-1}) \]  \hspace{1cm} (9.12) 

The \( n \)-steps-ahead predictor given in (9.9) requires future values of the \( m \) armband signals, \( \{\Delta \vartheta_{k+n-1}, \ldots, \Delta \vartheta_{k+n-1}\} \), which are assumed to be equal to the latest available armband measurements. Using (9.9), future glucose estimations over the entire prediction horizon, \( N_y \) and \( N_u \) in (5.7), can then be expressed in a notation given in (5.10) where the vector \( f \) is now a function of past input (i.e., insulin infusion rate), past output (i.e., CGM measurements) and past and current disturbance (i.e., \( m \)-armband measurements) variables.

The proposed multivariate closed-loop blood glucose regulation algorithm is described step-by-step as follows:

- **Step 0**: Decide on the model order (i.e., \( n_A, n_B, n_C, n_{\vartheta}^{(1)}, \ldots, n_{\vartheta}^{(m)} \) and \( d, d^{(1)}, \ldots, d^{(m)} \)) for the VARIMAX model in (9.1). Assign the design parameter values: \( N_y, N_u, q, r, u_{\text{min}}, u_{\text{max}}, \Delta_{\text{max}} \) in (5.17), and the initial values for \( \varphi_1, \) \( \hat{\theta}_0 \) in (9.7) and (9.8), respectively. Also, assign the value of \( \tau = 1/a \) in (5.2) and compute the \( P = P^n/P^d \) polynomial in (5.14).

- **Step 1**: Read the glucose measurement from the CGM device and the \( m \) signals from the armband.

- **Step 2**: For the model structure defined at Step 0, identify the VARIMAX model parameters (\( \hat{\theta}_k \)) using the weighted RLS and change detection methods.
described in Section 4.4 and Section 4.5, respectively.

- **Step 3:** Estimate the current blood glucose concentration using (5.14). And predict its future excursion using (9.9)-(9.12) and (5.16).

- **Step 4:** Using the strategy discussed in Section 5.5 and depicted in Figure 5.3, determine the reference glucose trajectory, \( \psi_{ref,k+j} \) in (5.17), that depends on the estimated current blood glucose value calculated at Step 3.

- **Step 5:** Using the variables calculated at Steps 3 and 4, solve the constrained quadratic optimization problem of (5.17), to obtain the vector of future insulin infusion rates, \( [\Delta u_k \ldots \Delta u_{k+N_u-1}] \).

- **Step 6:** Administer only the first insulin infusion rate, \( u_k = \Delta u_k + u_{k-1} \) from Step 5 to the patient.

- **Step 7:** Update \( \varphi_{k+1} \) in (9.7) to include the new measurements from Step 1, and update \( \hat{\theta}_k \) in (9.8) with its new value from Step 2. Then, return to Step 1

### 9.2 Subject Data

The protocol for the multivariate closed-loop experiment was reviewed and approved by the Institutional Review Boards of the University of Illinois at Chicago and the University of Chicago. Prior to participating in the study, the subject gave written informed consent. The study took place at the General Clinical Research Center (CRC) at the University of Chicago Hospitals.

One subject with type 1 diabetes (male, age 21 years, body mass index, BMI 23.1 kg/m\(^2\), diabetes duration > 10 years, total daily insulin dose 46±8 U) participated in two closed-loop experiments. Each experiment included 4-5.5 h of closed-loop glucose regulation during which the subject consumed a carbohydrate-rich meal and
performed high intensity exercise (i.e., 25 min run on a treadmill) 1-2 h prior to the food intake.

Insulin lispro (Humalog, Eli Lilly, Indianapolis, IN) was delivered using Paradigm Revel 723 insulin pump (Medtronic MiniMed, Northridge, CA), and the patient’s subcutaneous glucose concentrations were monitored with Guardian® REAL-Time CGM System (Medtronic MiniMed, Northridge, CA). The patient also wore a multi-sensor body monitor (BodyMedia SenseWear Pro3, Pittsburgh, PA) on the arm that provided real-time physiological measurements.

Subcutaneous glucose measurements were obtained every 10 min from the CGM device and entered manually into a graphical user interface on a computer. Real-time physiological measurements from the armband were wirelessly transmitted to the computer every 10 min. Basal insulin infusion rate calculated by the algorithm was then displayed on the computer screen and entered manually into the insulin pump. Each time, the calculated insulin rate was approved by a clinician before its administration to the patient. At any time, the clinician had the right to overrule the algorithm’s decision. In such a situation, the algorithm considered the actual insulin rate delivered when calculating the insulin rate for the next step.

9.3 Model Structure and Design Parameters

The VARIMAX model in (9.1) with constant model order (i.e., \(n_A, n_B, n_C, n_{\varphi}^{(1)}, \ldots, n_{\varphi}^{(m)}\) and \(d, d^{(1)}, \ldots, d^{(m)}\) all constant) is selected, and the model parameters in (9.8) are recursively identified at each sampling step. The model order \(n_B = 12\) and \(d = 3\) are selected based on pharmacokinetic profiles following subcutaneous injections of rapid-acting insulin as discussed in Section 7.3. Additionally, \(n_A = 2\), \(n_C = 1\) is used. Only 5 out of the 7 signals from the armband are found to have significant effect on a patient’s glucose excursions in Chapter 8. For these signals,
where \( m = 5 \) and \([\vartheta_k^{(1)}, \ldots, \vartheta_k^{(m)}] = [EE_k, LA_k, HF_k, GSR_k, BT_k]\), the model order of \([n_\vartheta^{(1)}, \ldots, n_\vartheta^{(m)}] = [1, 1, 2, 2, 2]\) is selected, and \([d^{(1)}, \ldots, d^{(m)}] = [4, 4, 5, 7, 5]\) is used based on the results discussed in Chapter 8.

Besides the model order, other tuning parameters used by the algorithm include the window size, \( N_W \), and the regular and the reduced values for the forgetting factor, \( \lambda \). These parameters and the model order are kept constant and therefore do not require tailoring for each subject. Window size is set to 20 min (i.e., \( N_W = 2 \) steps), and \( \lambda = 0.5 \) is used. When a change in model parameters is detected the value of \( \lambda \) is reduced to 0.005. Past glucose and physiological measurements required for the initialization of \( \varphi_{k=0} \) in (9.7) are set to patient’s first measurements from the CGM sensor and the armband, respectively. Additionally, the past insulin infusion rates and the past residual terms in (9.7) are set to zero. The initial model parameters, \( \hat{\theta}_{k=0} \) in (9.8), are assigned to zero except \( \hat{b}_{0,k=0} \) and \( \{\hat{h}_{0,k=0}^{(1)}, \ldots, \hat{h}_{0,k=0}^{(m)}\} \) which are set to 1.

Other controller design parameters include the weight on input and output terms in the quadratic cost functions of GPC, \( q \) and \( r \) in (5.17), respectively. A ratio of \( q/r = 5 \) is selected. In addition to the exponential reference trajectory described in Section 5.5, the effort on trajectory tracking during hypoglycemia is increased by increasing the \( q/r \) ratio by 3-fold for glucose concentrations below 80 mg/dl. Prediction horizons for control input and output of GPC, \( N_u \) and \( N_y \) in (5.17), are set to 5 and 6 (i.e., 50 and 60 min), respectively. And a constant time-delay between subcutaneous and blood glucose concentrations is assumed with \( \tau = 5 \) set in (5.2).

9.4 Closed-Loop Results

The closed-loop setup consists of four components; (i) a CGM device, (ii) a
multi-sensor body monitor, (iii) an insulin pump, and (iv) a computer. The control algorithm is implemented on a MATLAB (MathWorks Inc., Natick, MA) graphical user interface (GUI). The control algorithm is initialized with a user-specified maximum allowable insulin infusion rate, $u_{\text{max}}$ in (5.17), and the first measurements from the CGM device and the armband. Thereafter, the algorithm uses the CGM and armband measurements every 10 min as the only input and displays the calculated insulin infusion rate on the GUI. Each time, the calculated insulin rate is approved by a clinician before it is delivered to the patient. If at any time, insulin other than the one displayed on the GUI is administered (e.g., the clinician overrules the algorithm’s decision, or enters a wrong rate on the pump by mistake), the algorithm considers the actual insulin rate delivered when calculating the rate for the next step. No such case has occurred during the two closed-loop experiments performed.

The performance of the multivariate control algorithm is evaluated with two clinical experiments performed on a patient with type 1 diabetes during a meal and a physical activity challenge as described in Section 9.2. The first closed-loop experiment was conducted from 1:40PM till 5:38PM and was initialized with $u_{\text{max}} = 10U/h$. Before closing the loop, the subject ate breakfast with 50 g carbohydrate content and delivered a manual premeal bolus of 8.2 U at 10:37AM. The subject then performed high intensity running workout on a treadmill for 25 min (12:15PM-12:40PM), and consumed a carbohydrate-rich lunch at 1:30PM.

Glucose regulation during the closed-loop period is demonstrated in Figure 9.2. The patient’s venous glucose concentrations were not obtained during the study, therefore, only the measurements from the CGM device and fingerstick values, if any, are displayed. Figure 9.3 shows the basal insulin adjustments commanded by the multivariate control algorithm developed.

From the high premeal levels of 185 mg/dl, the patient’s glucose concentrations
increase to 256 mg/dl as shown in Figure 9.2, with maximum peak occurring at around 3PM (i.e., 1.5 h after lunch). Glucose concentrations then return to premeal levels within 2.5 h of the meal time, at 4PM. Within shortly, at 4:30PM, only 3 h after the lunch, the controller achieves and maintains normoglycemia (i.e., 120-70 mg/dl). The effectiveness of the closed-loop algorithm developed is also obvious from its quick response to increase in glucose levels as shown in Figure 9.3. Similarly, it
responds quickly during the fall in glucose concentrations, and commands only 0.1 $U/h$ of insulin when glucose returns to its premeal level (i.e., 185 mg/dl) despite the fact that it is above the normoglycemic range. At 5PM, even though the CGM device was reading 82 mg/dl (i.e., normoglycemia), a fingerstick value of 54 mg/dl (i.e., hypoglycemia) was obtained and the patient was treated with a carbohydrate drink. This hypoglycemia was probably caused by the high maximum insulin setting, $u_{max} = 10 U/hr$, that lead to accumulated insulin in the patient’s body. Another contributor to the hypoglycemia might be the fact that the CGM sensor was not calibrated according to the manufacturer’s specifications that day. This might have caused biased high CGM measurements and therefore the high insulin rates.

Figures 9.4-9.8 show the energy expenditure, average longitudinal acceleration, heat flux, galvanic skin response and near-body temperature values measured by the armband, and used by the control algorithm during the closed-loop experiment. Since, the closed-loop period excluded the exercise performed at 12:15PM, and afterwards the patient remained mostly sedentary, the energy expenditure in Figure 9.4 remains at low levels. Figures 9.6 and 9.8 show that the heat flux increased and the near-body temperature decreased when the patient was experiencing hypoglycemia at around 4:30PM-5PM.

The second closed-loop experiment was performed the next day and on the same patient. Because of the postmeal hypoglycemia experienced during the first closed-loop study, the maximum insulin infusion setting was reduced by half to $u_{max} = 5 U/h$, and the CGM sensor was properly calibrated according to the manufacturer’s specifications on the second day. The experiment was conducted from 10:20AM till 3:45PM and included the time period where the subject performed exercise.
Figure 9.4. Energy expenditure measured by the armband and used by the control algorithm during the first closed-loop experiment.

Figure 9.5. Average longitudinal acceleration measured by the armband and used by the control algorithm during the first closed-loop experiment.
Figure 9.6. Heat flux measured by the armband and used by the control algorithm during the first closed-loop experiment.

Figure 9.7. Galvanic skin response measured by the armband and used by the control algorithm during the first closed-loop experiment.
Before closing the loop, the subject ate breakfast at around 8:30AM and his insulin was adjusted manually. Approximately one hour after closing the loop, the subject performed the high intensity treadmill running (11:30AM-11:55AM) and subsequently consumed a carbohydrate-rich lunch at 12:40PM.

Glucose regulation during the second closed-loop experiment is demonstrated in Figure 9.9. Figure 9.10 shows the basal insulin adjustments commanded by the algorithm during this period. From premeal level at 210 $mg/dl$, glucose concentrations rise to 290 $mg/dl$ in Figure 9.9. Maximum postmeal peak occurs at 2:30PM, and glucose concentrations return to premeal levels within 3 $h$ of the meal time. Insulin infusion rates remain low before the lunch and start to increase with the postmeal increase in glucose levels. Because of the reduced maximum insulin setting (i.e., $u_{\text{max}} = 5$ $U/h$), control algorithm in Figure 9.10 is less aggressive to respond to postmeal rise in glucose compared to Figure 9.3. Still, comparable control performance is achieved with both $u_{\text{max}}$ settings. For instance, the net postmeal glucose increase is
71 mg/dl and 80 mg/dl during the first and second experiments as shown in Figures 9.2 and 9.9, respectively. And the time to achieve premeal glucose levels is 2.5 hours and 3 hours with the high and low $u_{max}$ settings in Figures 9.2 and 9.9, respectively.

Figure 9.9. Glucose concentrations during the second closed-loop experiment.

Figure 9.10. Basal insulin infusion rates commanded by the multivariate control algorithm during the second closed-loop experiment.

Due to the hospital’s patient discharge protocol, the second experiment was cut short, and included only 3 hours of postmeal period compared to the 4 hours during the first closed-loop experiment. Within this 3 hour period, the controller achieved
postmeal glucose levels, but did not have enough time to normalize the patient’s glucose concentrations from the very high premeal levels (i.e., 210 mg/dl).

Table 9.1 compares the glucose regulation during the two closed-loop experiments. The total insulin delivered during the first experiment that lasted 3.95 h is 16.59 U and 99% (i.e., 16.48 U) of it is delivered within 3 h after the meal. During the second experiment, total insulin delivered reduces to 13.01 U despite the longer closed-loop period (i.e., 5.44 h). This is due to the decreased maximum insulin setting, \( u_{\text{max}} \), which also leads to significantly reduced insulin delivery within 3 h of meal time (11.43 U versus 16.48 U).

Table 9.1. Glucose regulation during the two closed-loop experiments

<table>
<thead>
<tr>
<th></th>
<th>Experiment Number 1</th>
<th>Experiment Number 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controller Setting - ( u_{\text{max}} ) (U/h)</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Closed-loop Duration (h)</td>
<td>3.95</td>
<td>5.44</td>
</tr>
<tr>
<td>Premeal Glucose (mg/dl)</td>
<td>185</td>
<td>210</td>
</tr>
<tr>
<td>Postmeal Glucose Peak (mg/dl)</td>
<td>256</td>
<td>290</td>
</tr>
<tr>
<td>Time to Return to Premeal Glucose (h)</td>
<td>2.5</td>
<td>3</td>
</tr>
<tr>
<td>Total Insulin Delivered (U)</td>
<td>16.59</td>
<td>13.01</td>
</tr>
<tr>
<td>Insulin Delivered within 3 h after Meal (U)</td>
<td>16.48</td>
<td>11.43</td>
</tr>
<tr>
<td>Glucose(_{\text{avg}}) ± SD (mg/dl)</td>
<td>169±63</td>
<td>238±27</td>
</tr>
<tr>
<td>[Glucose(<em>{\text{min}}), Glucose(</em>{\text{max}})] (mg/dl)</td>
<td>[72, 256]</td>
<td>[200, 290]</td>
</tr>
</tbody>
</table>

avg - average, SD - standard deviation, min - minimum, and max - maximum.

Figures 9.11-9.15 show the energy expenditure, average longitudinal acceleration, heat flux, galvanic skin response and near-body temperature values measured by the armband, and used by the control algorithm during the second closed-loop experiment. Increase in the energy expenditure, heat flux and galvanic skin response during exercise is evident in Figures 9.11, 9.13 and 9.14, respectively. On the other hand, the average longitudinal acceleration in Figure 9.12 and the near-body temperature...
in Figure 9.15 slightly decrease during and post exercise, respectively.

Figure 9.11. Energy expenditure measured by the armband and used by the control algorithm during the second closed-loop experiment.

Figure 9.12. Average longitudinal acceleration measured by the armband and used by the control algorithm during the second closed-loop experiment.
Figure 9.13. Heat flux measured by the armband and used by the control algorithm during the second closed-loop experiment.

Figure 9.14. Galvanic skin response measured by the armband and used by the control algorithm during the second closed-loop experiment.
Table 9.2 reports the mean energy expenditure, average longitudinal acceleration, heat flux, galvanic skin response, and near-body temperature values during the two closed-loop experiments. It also includes the minimum and maximum values of the five armband signals observed during the closed-loop periods. Compared to the first closed-loop experiment, maximum values of energy expenditure, heat flux, and galvanic skin response are significantly higher during the second study which included the exercise period.

9.5 Conclusions

The univariate control algorithm for fully automated blood glucose regulation that is developed and evaluated in Chapter 5 and Chapter 7, respectively, is extended to a multivariate algorithm that uses not only a patient’s glucose measurements from a CGM device, but also several physiological signals depicting the patient’s physical activity and emotional conditions. Such physiological signals are shown to have a
Table 9.2. Glucose regulation during the two closed-loop experiments

<table>
<thead>
<tr>
<th></th>
<th>Experiment Number 1</th>
<th>Experiment Number 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Includes Exercise Period (Y/N)</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>EE$_{avg}$ ± SD ($kcal/min$)</td>
<td>1.15±0.17</td>
<td>1.78±1.38</td>
</tr>
<tr>
<td>[EE$<em>{min}$, EE$</em>{max}$] ($kcal/min$)</td>
<td>[0.90, 1.46]</td>
<td>[0.90, 8.78]</td>
</tr>
<tr>
<td>LA$_{avg}$ ± SD ($m/s^2$)</td>
<td>0.30±0.63</td>
<td>0.50±0.57</td>
</tr>
<tr>
<td>[LA$<em>{min}$, LA$</em>{max}$] ($m/s^2$)</td>
<td>[-0.99, 0.96]</td>
<td>[-0.85, 0.98]</td>
</tr>
<tr>
<td>HF$_{avg}$ ± SD ($W/m^2$)</td>
<td>90.77±9.89</td>
<td>93.64±21.71</td>
</tr>
<tr>
<td>[HF$<em>{min}$, HF$</em>{max}$] ($W/m^2$)</td>
<td>[70.34, 107.85]</td>
<td>[49.96, 167.12]</td>
</tr>
<tr>
<td>GSR$_{avg}$ ± SD ($\mu S$)</td>
<td>1.39±0.33</td>
<td>1.72±0.92</td>
</tr>
<tr>
<td>[GSR$<em>{min}$, GSR$</em>{max}$] ($\mu S$)</td>
<td>[1.06, 2.23]</td>
<td>[0.40, 4.06]</td>
</tr>
<tr>
<td>BT$_{avg}$ ± SD ($^0 C$)</td>
<td>32.59±0.43</td>
<td>33.50±0.36</td>
</tr>
<tr>
<td>[BT$<em>{min}$, BT$</em>{max}$] ($^0 C$)</td>
<td>[31.82, 33.39]</td>
<td>[32.29, 34.16]</td>
</tr>
</tbody>
</table>

EE - energy expenditure, LA - longitudinal acceleration, HF - heat flux, GSR - galvanic skin response, BT - near-body temperature, avg - average, SD - standard deviation, min - minimum, and max - maximum.

significant effect on a patient’s glucose metabolism in Chapter 8. In this thesis, physiological signals are collected with a multi-sensor body monitor worn on the arm. At each sampling step (e.g., 10 min), the measurements from the glucose sensor and the body monitor are inputted to the multivariate control algorithm developed which then computes the required basal insulin infusion rate for the patient.

An adaptive model-based control algorithm that utilizes GPC theory has been developed. The adaptability of the controller is provided with recursive subject-specific glucose prediction models that use recent history of CGM and armband data and previous basal insulin infusion rates. At each sampling step, model parameters are updated to include the patient’s most recent glucose dynamics. The identified model is then used to predict the patient’s future glucose excursions and is integrated with the control algorithm developed for calculating the appropriate control action (i.e., insulin infusion rate). The optimal insulin rate is determined by solving
an optimization problem that minimizes the deviation of predicted glucose values from a desired reference glucose trajectory. Since the subcutaneous route for both glucose sensing and insulin delivery is considered, two delay compensators are also introduced to the control algorithm, in order to account for the time-lag between subcutaneous and blood glucose concentrations, and delays in insulin action due to its slow absorption from subcutaneous tissue.

The closed-loop algorithm developed does not require any patient specific tailoring or prior experimental data before implementation. The maximum allowable insulin infusion rate, \( u_{\text{max}} \), is the only user-specified variable used to initialize the algorithm. The algorithm is also designed to function in a fully automated manner and does not require any prior disturbance announcements or information. Therefore, it can easily be implemented for any patient using a CGM sensor and a multi-sensor body monitor.

The performance of the controller has been tested with two clinical experiments performed on a patient with type 1 diabetes during a high intensity exercise followed with a carbohydrate-rich meal challenge. Since venous blood glucose measurements were not obtained during the two studies, the performance was evaluated using the CGM device measurements.

The first closed-loop experiment was initialized with \( u_{\text{max}} = 10 \, U/hr \), while \( u_{\text{max}} = 5 \, U/hr \) was used during the second experiment. With both settings, the controller succeeded to return the patient’s glucose concentrations back to premeal levels within 2.5-3 h after the meal consumption, and more importantly it achieved this with low net postmeal glucose increase (i.e., 70-80 mg/dl). Normoglycemia was achieved during the first closed-loop experiment. However, the shorter postmeal period during the second experiment, was not long enough to evaluate the algorithm for normalizing the patient’s glucose concentrations from the very high premeal levels
A late postmeal hypoglycemia (i.e., 54 mg/dl) was detected with a finger-stick measurement during the first closed-loop experiment. However, during this hypoglycemic period, the lowest CGM measurement (i.e., 72 mg/dl) was still in the normoglycemic range. The failure of detecting the hypoglycemia with the CGM device may be contributed to the fact that the sensor was not calibrated according to the manufacturer’s specifications that day. This might have lead to artificially high CGM sensor measurements, and consequently high insulin rates which caused the hypoglycemia observed.
A subject-specific data-driven modeling algorithm for predicting a subject’s future glucose concentrations has been developed. In Chapter 6, it has been shown that glucose concentrations can be predicted using recent history of continuous glucose monitoring (CGM) data only. The univariate modeling algorithm developed is extended to a multivariate one in Chapter 8, where a subject’s CGM data is supplemented with several physiological measurements from a multi-sensor body monitor worn on the arm and that are known to have a significant effect of the whole-body fuel metabolism. Glucose prediction accuracy is shown to improve with the multivariate modeling algorithm.

Estimation of future glucose concentrations is a crucial task for diabetes management. With the current therapy, it is generally difficult to estimate future glucose levels and therefore to determine the required corrective action for the patients. Both the univariate and the multivariate subject-specific modeling algorithms developed in this thesis can simplify management with diabetes. For instance, predicted glucose concentrations can be used to provide early hypoglycemia or hyperglycemia alarms that allow patients to take corrective actions. Predicted glucose values can also guide patients with their daily insulin dose decisions and adjustments. Additionally, the algorithms developed can be integrated with a model-based control algorithm to build a fully automated artificial pancreas.

An adaptive model-based closed-loop algorithm has also been developed in this thesis to provide fully automated blood glucose regulation with subcutaneous insulin delivery. In Chapter 7, the control algorithm that utilizes the univariate modeling algorithm developed is shown to keep a patient’s glucose levels within tight control with simulation studies. The univariate control algorithm is extended to a
multivariate one in Chapter 9 to include the signals from the armband, and is tested in vivo with two clinical closed-loop experiments.

The long-term complications of diabetes (e.g., diabetic ketoacidosis, kidney failure, and cardiovascular diseases) can be reduced by controlling a patient’s blood glucose concentrations within normoglycemic limits. Current therapy with insulin injections or a manual pump restricts patients to follow a rigid lifestyle, and it may lead to prolonged hyperglycemia or hypoglycemia, since it is difficult for the patient to decide on the optimal insulin amount/rate and correct timing of injection/infusion with changing daily life conditions (e.g., diet, exercise, stress or illness). Therefore, closing the glucose regulation loop with the fully automated control algorithms developed in this thesis will revolutionize management with diabetes and significantly improve the quality of lives of the patients.

One of the main contributions of this thesis is the subject-specific adaptive modeling strategy that does not require any physiological representation of glucose-insulin dynamics or disturbance modeling. Most of the proposed model predictive control strategies in the literature utilize physiological models which are nonlinear and hard to tune at each sampling step. Such systems also require models representing insulin absorption from subcutaneous tissue and absorption of ingested glucose from gastrointestinal tract (i.e., disturbance model). Selection of a proper physiological model is also an issue, as the controller performance is strongly dependent on the accuracy of the model to represent the true dynamics of the system.

Glycemic disturbances encountered during daily life and a subject’s glucose metabolism can be variable and unpredictable. The proposed modeling and control algorithms can dynamically monitor and reject such variable dynamic behavior and different types of glycemic disturbances without requiring any prior information about the disturbance. A change detection method has been specifically designed and
integrated to the modeling algorithm to improve the predictions in presence of any change in blood glucose caused by any type of disturbance or metabolic behavior.

Adding inputs such as meal size and time, or exercise intensity to the model will further improve the glucose prediction accuracy. However, it will necessitate manual inputs provided by the patient. In this research, the focus has been on algorithms that do not require any patient intervention or involvement, in order to provide a patient with total freedom in his/her daily life. Both the CGM data and the armband signals are wirelessly acquired by the algorithms developed; thus, the effect of physical activity is captured without requiring any patient intervention.

None of the algorithms developed in this thesis require any patient specific tailoring or prior experimental data before implementation. They are also designed to function in a fully automated manner and do not require any disturbance announcements or manual inputs. Therefore, they are good candidates for installation on a portable ambulatory device used in a patient’s home environment for his/her diabetes management.

Another novelty of this research is that the two time-delays (i.e., delay in control action and delay between measured and controlled variables) associated with glucose control are explicitly expressed in the formulations of the controller structure. The univariate and the multivariate control algorithms developed are designed and evaluated for the subcutaneous route for both glucose sensing and insulin delivery. However, modification/application of the algorithms to any other insulin delivery and glucose measurement route is straightforward as it will require only the adjustment of the values that describe the time-delays. In contrast, adjustment of control algorithms that utilize physiological models will require a new physiological model for each glucose-insulin route.
The algorithms developed assume availability of a CGM device and a multi-sensor body monitor that both provide accurate measurements. CGM sensors are not yet widely adopted among patients with diabetes, and their main use is currently limited to clinical studies. Therefore, widespread real life implementation of the algorithms developed currently may be limited. However, development of reliable CGM technologies is an extensively on-going research, and current limitations with such devices will most probably be solved in the near future.

The closed-loop algorithms developed should also be tested and validated on a large and diverse population with type 1 diabetes under free living conditions and different glycemic challenges, before their widespread real life implementation.
AIC  Akaike information criterion
AR   Autoregressive model
ARX  Autoregressive exogenous input model
ARMA Autoregressive moving average model
ARMAX Autoregressive moving-average model with exogenous inputs
ARIMAX Autoregressive integrated moving-average model with exogenous inputs
AUC  Area under the curve
BG   Blood glucose
CGM  Continuous glucose monitoring
CG-EGA Continuous glucose error grid analysis
CHO  Carbohydrate
DCCT Diabetes control and complications trial
GPC  Generalized predictive control
IVGTT Intravenous glucose tolerance test
KF   Kalman filter
LQC  Linear quadratic control
LR   Likelihood ratio
MA   Moving average model
MISO Multiple-input-single-output
MM   Minimal model
MPC  Model predictive control
NN   Neural network
OGTT Oral glucose tolerance test
PD   Proportional-derivative controller
PH   Prediction horizon
PID  Proportionalintegralderivative controller
RAD  Relative absolute deviation
RLS  Recursive least squares
SMBG Self monitored blood glucose
SSD  Sum of squared deviations
SSGPE Sum of squares of the glucose prediction error
UKPDS United Kingdom prospective diabetes study
VARMA Vector ARMA model
VARMAX Vector ARMAX model
APPENDIX B
MODELS FOR VIRTUAL PATIENT SIMULATION
B.1 Model of GlucoSim

Model of GlucoSim [5], [86] considers the pharmacokinetic diagrams of insulin and glucose demonstrated by Figures B.1 and B.2, respectively. The body is divided into several compartments. In terms of physiology, each compartment represents the primary body organs associated with the regulation of glucose or insulin. Moreover, the compartment (i.e., organ) itself can be divided into two or more regions if there are mass transfer limitations within the compartment. Material balance is written around each compartment, resulting in a set of differential equations which are solved simultaneously.

Glucose Model:

Figure B.1. Pharmacokinetic diagram of the glucose model [5].
Circulating Blood:

\[
\frac{dG_B}{dt} = \frac{Q_{GH} (G_B - G_H) + Q_{GK} (G_K - G_B) + Q_{GNS} (G_{NS} - G_B)}{V_{GB}} + \frac{Q_{GPR} (G_{PR} - G_B) + Q_{GL} G_L - (Q_{GH_A} + Q_{GPN} + Q_{GT}) G_B}{V_{GB}}
\]  
(B.1)

Kidney:

\[
\frac{dG_K}{dt} = \frac{Q_{GK} (G_B - G_K) - KGU - GE}{V_{GK}}
\]  
(B.2)

Nervous System:

\[
\frac{dG_{NS}}{dt} = \frac{Q_{GNS} (G_B - G_{NS}) - NGU}{V_{GNS}}
\]  
(B.3)

Periphery:

\[
\frac{dG_{PR}}{dt} = \frac{Q_{GPR} (G_B - G_{PR}) - PRGU}{V_{GPR}}
\]  
(B.4)

Pancreas & Spleen:

\[
\frac{dG_{PN}}{dt} = \frac{Q_{GPN} (G_B - G_{PN})}{V_{GPN}}
\]  
(B.5)

Gastro-Intestinal Tract:

\[
\frac{dG_{GT}}{dt} = \frac{Q_{G_{GT}} (G_B - G_{GT}) + GA}{V_{G_{GT}}}
\]  
(B.6)

Heart:

\[
\frac{dG_H}{dt} = \frac{Q_{GH} (G_B - G_H) - HGU}{V_{G_H}}
\]  
(B.7)

Liver:

\[
\frac{dG_L}{dt} = \frac{Q_{GH_A} G_B + Q_{GPN} G_{PN} + Q_{G_{GT}} G_{GT} - Q_{G_L} G_L - LGU - LGP}{V_{G_L}}
\]  
(B.8)
Glucose Utilization Functions:

\[ TGU = k \, I_A \, G_B + CNU \left( 1 - e^{-G_B/bw} \right) \]  

(B.9)

\[ \frac{dI_A}{dt} = \frac{1}{T_{IA}} \left( I_{BD} - I_A \right) \quad I_A(t = 0) = I_{B0} \]  

(B.10)

\[ CNU \approx constant \]  

(B.11)

\[ KGU = 0.07 \, TGU \]  

(B.12)

\[ PRGU = 0.5 \, TGU \]  

(B.13)

\[ HGU = 0.01 \, TGU \]  

(B.14)

\[ LGU = 0.4 \, TGU \]  

(B.15)

Glucose Excretion from Kidney:

\[ GE = 1.25 \frac{dl}{min} \left( G_B - 176 \frac{mg}{dl} \right) U \left( G_B - 176 \frac{mg}{dl} \right) \]  

(B.16)

Glucose Absorption from the Intestine:

\[ \frac{dGA}{dt} = -\frac{1}{T_A}GA + \frac{F}{T_A \, T_{GE}}G_G \quad GA(t < t_m) = 0 \]  

(B.17)

\[ \frac{dG_G}{dt} = -\frac{1}{T_{GE}}G_G + CHO_G \quad G_G(t < t_M) = 0 \]  

(B.18)

Liver Glucose Production:

\[ LGP = a_1 \left( 1 - \frac{a_2 (G_D - a_3)}{|G_D - a_3| + a_4} \right) \]  

(B.19)
\[
\frac{dG_{ID}}{dt} = \begin{cases} 
    k_A (G_{LD} I_{BD} - G_{ID}) & \text{if } \frac{d}{dt}G_{LD} I_{BD} \geq 0 \\
    k_D (G_{LD} I_{BD} - G_{ID}) & \text{if } \frac{d}{dt}G_{LD} I_{BD} < 0 
\end{cases} 
\]

\(G_{ID}(t = 0) = G_{I0} I_{BD}\)  \(\text{(B.20)}\)

Insulin Model:

![Pharmacokinetic diagram of the insulin model](image)

Figure B.2. Pharmacokinetic diagram of the insulin model [5].
Circulating Blood:

\[
d\frac{I_B}{dt} = \frac{Q_{ISc}(I_{SC} - I_B) + Q_{IK}(I_K - I_B) + Q_{IPR}(I_{PR} - I_B)}{V_{IB}} + \frac{Q_{IL} I_L - (Q_{IHA} + Q_{IPN} + Q_{IGT}) I_B}{V_{IB}} \tag{B.21}
\]

Kidney:

\[
d\frac{I_K}{dt} = \frac{Q_{IK}(I_B - I_K) - KIR}{V_{IK}} \tag{B.22}
\]

Subcutaneous Tissue:

\[
d\frac{I_{SC}}{dt} = \frac{Q_{ISc}(I_B - I_{SC}) + I_A}{V_{ISc}} \tag{B.23}
\]

Periphery:

\[
d\frac{I_{PR}}{dt} = \frac{Q_{IPR}(I_B - I_{PR}) - PRIR}{V_{IPR}} \tag{B.24}
\]

Pancreas & Spleen:

\[
d\frac{I_{PN}}{dt} = \frac{Q_{IPN}(I_B - I_{PN})}{V_{IPN}} \tag{B.25}
\]

Gastro-Intestinal Tract:

\[
d\frac{I_{GT}}{dt} = \frac{Q_{IGT}(I_B - I_{GT})}{V_{IGT}} \tag{B.26}
\]

Liver:

\[
d\frac{I_L}{dt} = \frac{Q_{IHA} I_B + Q_{IPN} I_{PN} + Q_{IGT} I_{GT} - Q_{IL} I_L - LIR}{V_{IL}} \tag{B.27}
\]

Insulin Removal Functions:

\[
KIR = 0.35 \, Q_{IK} \, I_K \tag{B.28}
\]

\[
PRIR = 0.15 \, Q_{IPR} \, I_{PR} \tag{B.29}
\]

\[
LIR = 0.5 \, Q_{IL} \, I_L \tag{B.30}
\]
Subcutaneous Insulin Absorption:

\[
\frac{dI_P}{dt} = -\frac{1}{\tau_P} I_P, \quad I_P(t = 0) = \frac{I_P(0)}{V_B} \tag{B.31}
\]

\[
\frac{dI_S}{dt} = \frac{1}{\tau_P} I_P - \frac{1}{\tau_S} I_S, \quad I_S(t = 0) = I_{S0} \tag{B.32}
\]

\[
\frac{dI_B}{dt} = \frac{1}{\tau_S} I_S - \frac{1}{\tau_B} I_B, \quad I_B(t = 0) = I_{B0} \tag{B.33}
\]

Flow Rates:

<table>
<thead>
<tr>
<th>Total Flow Rate for a Specific Compartment</th>
<th>Flow Rate of Glucose for a Specific Compartment</th>
<th>Flow Rate of Insulin for a Specific Compartment</th>
</tr>
</thead>
<tbody>
<tr>
<td>( Q_{tK} = \frac{100}{60} Q_{IK} )</td>
<td>( Q_{GK} = \frac{84}{100} Q_{IK} )</td>
<td>( Q_{IK} = \frac{9.9314 \text{ bw} + 0.6859}{100} )</td>
</tr>
<tr>
<td>( Q_{INS} = \frac{10.9}{18.8} Q_{IK} )</td>
<td>( Q_{GNS} = \frac{84}{100} Q_{INS} )</td>
<td>( Q_{INS} = \frac{60}{100} Q_{INS} )</td>
</tr>
<tr>
<td>( Q_{IPR} = \frac{21.8}{18.8} Q_{IK} )</td>
<td>( Q_{GPR} = \frac{84}{100} Q_{IPR} )</td>
<td>( Q_{IPR} = \frac{60}{100} Q_{IPR} )</td>
</tr>
<tr>
<td>( Q_{tHA} = \frac{5}{18.8} Q_{IK} )</td>
<td>( Q_{GHA} = \frac{84}{100} Q_{tHA} )</td>
<td>( Q_{tHA} = \frac{60}{100} Q_{tHA} )</td>
</tr>
<tr>
<td>( Q_{IGT} = Q_{IK} )</td>
<td>( Q_{GGT} = \frac{84}{100} Q_{IGT} )</td>
<td>( Q_{IGT} = \frac{60}{100} Q_{IGT} )</td>
</tr>
<tr>
<td>( Q_{IPN} = \frac{40}{100} Q_{IK} )</td>
<td>( Q_{GPN} = \frac{84}{100} Q_{IPN} )</td>
<td>( Q_{IPN} = \frac{60}{100} Q_{IPN} + \frac{8}{100} Q_{IL} )</td>
</tr>
<tr>
<td>( Q_{IPV} = Q_{IPN} + Q_{IGT} )</td>
<td>( Q_{GPV} = \frac{84}{100} Q_{IPV} )</td>
<td>( Q_{IPV} = \frac{60}{100} Q_{IPV} )</td>
</tr>
<tr>
<td>( Q_{IL} = Q_{tHA} + Q_{IPV} )</td>
<td>( Q_{GL} = \frac{84}{100} Q_{IL} )</td>
<td>( Q_{IL} = \frac{60}{100} Q_{IL} )</td>
</tr>
<tr>
<td>( Q_{GH} = Q_{GNS} + Q_{GL} + Q_{GK} + Q_{GPR} )</td>
<td>( Q_{ISC} = \frac{Q_{IK}}{10} )</td>
<td></td>
</tr>
</tbody>
</table>

Table B.1. Flow Rates
Volumes:

Total volume for circulating blood:  \[ V_{tB} = \frac{100}{60} V_{iB} \]

<table>
<thead>
<tr>
<th>Glucose Volume for a Specific Compartment</th>
<th>Insulin Volume for a Specific Compartment</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_{GB} = \frac{84 V_{iB}}{100} )</td>
<td>( V_{iB} = \frac{44 bm^{0.99}}{100} )</td>
</tr>
<tr>
<td>( V_{GK} = \frac{12.2 V_{GB}}{100} )</td>
<td>( V_{IK} = \frac{60 V_{GK}}{84} )</td>
</tr>
<tr>
<td>( V_{GNS} = \frac{7.44 V_{GB}}{100} )</td>
<td>( V_{INS} = \frac{60 V_{GNS}}{84} )</td>
</tr>
<tr>
<td>( V_{GPR} = \frac{22.32 V_{GB}}{100} )</td>
<td>( V_{IPR} = \frac{60 V_{GPR}}{84} )</td>
</tr>
<tr>
<td>( V_{GH} = \frac{29.17 V_{GB}}{100} )</td>
<td>( V_{IH} = \frac{60 V_{GH}}{84} )</td>
</tr>
<tr>
<td>( V_{GGT} = \frac{12.8 V_{GB}}{100} \times \frac{60}{100} )</td>
<td>( V_{IGT} = \frac{60 (V_{GGT}+V_{GPN})}{84} )</td>
</tr>
<tr>
<td>( V_{GPN} = \frac{12.8 V_{GB}}{100} \times \frac{40}{100} )</td>
<td>( V_{IPN} = \frac{60 V_{GL}}{84} \times \frac{1}{2} )</td>
</tr>
<tr>
<td>( V_{GL} = \frac{26.07 V_{GB}}{100} )</td>
<td>( V_{IL} = \frac{60 V_{GL}}{84} \times \frac{1}{2} )</td>
</tr>
<tr>
<td></td>
<td>( V_{ISC} = \frac{V_{GPN}+V_{GL}}{10} )</td>
</tr>
</tbody>
</table>
Other Parameters:

Table B.3. Model Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k$</td>
<td>0.0042 $(dl/\mu U \ kg \ min)$</td>
</tr>
<tr>
<td>$CNU$</td>
<td>1.87 $(mg/kg \ min)$</td>
</tr>
<tr>
<td>$T_{D,TGU}$</td>
<td>30 $(min)$</td>
</tr>
<tr>
<td>$T_{IA}$</td>
<td>31.2 $(min)$</td>
</tr>
<tr>
<td>$T_A$</td>
<td>48.66 $(min)$</td>
</tr>
<tr>
<td>$T_{GE}$</td>
<td>156.59 $(min)$</td>
</tr>
<tr>
<td>$F$</td>
<td>1.0 (unitless)</td>
</tr>
<tr>
<td>$a_1$</td>
<td>1.13 $(mg/kg \ min)$</td>
</tr>
<tr>
<td>$a_2$</td>
<td>0.43 $(mg/kg \ min)$</td>
</tr>
<tr>
<td>$a_3$</td>
<td>725900 $(mg \ \mu U/dl)$</td>
</tr>
<tr>
<td>$a_4$</td>
<td>40000 $(mg \ \mu U/dl)$</td>
</tr>
<tr>
<td>$k_A$</td>
<td>0.3671 $(min^{-1})$</td>
</tr>
<tr>
<td>$k_D$</td>
<td>0.0036 $(min^{-1})$</td>
</tr>
<tr>
<td>$\tau_p = \tau_S = \tau_B$</td>
<td>110 $(min)$</td>
</tr>
<tr>
<td>$c_1$</td>
<td>1000 $(\mu U/min)(mg/dl)^{-1}$</td>
</tr>
<tr>
<td>$c_2$</td>
<td>2000 $(\mu U/min)(mg/dl)^{-1}$</td>
</tr>
<tr>
<td>$T_1$</td>
<td>12 $(min^{-1})$</td>
</tr>
<tr>
<td>$T_2$</td>
<td>2 $(min^{-1})$</td>
</tr>
<tr>
<td>$c_p = \frac{K_p}{T_1}$</td>
<td>$8.3 \ e^{-5GB} + 2.3 \ e^{-2}$</td>
</tr>
<tr>
<td>$c_d = \frac{T_d}{T_2}$</td>
<td>$7.2 \ e^{-3GB} + 1.2$</td>
</tr>
</tbody>
</table>
### Nomenclature:

#### Variables:
- **G**: Glucose Concentration ($mg/dl$)
- **I**: Insulin Concentration ($U/dl$)
- **Q**: Blood Flow Rate ($dl/min$)
- **V**: Volume ($dl$)
- **t**: Time ($min$)
- **r**: Metabolic Source or Sink Rate ($mg/min$)

#### Subscripts:
- **B**: Blood
- **HA**: Hepatic Artery
- **K**: Kidney
- **NS**: Nervous System
- **PR**: Periphery
- **PN**: Pancreas and Spleen
- **PV**: Portal Vein
- **GT**: Gastrointestinal Tract
- **H**: Heart
- **L**: Liver
- **SC**: Subcutaneous Tissue

#### Metabolic Rates:
- **KGU**: Kidney Glucose Utilization
- **NSGU**: Nervous System Glucose Utilization
- **HGU**: Heart Glucose Utilization
- **LGU**: Liver Glucose Utilization
- **PRGU**: Periphery Glucose Utilization
- **LGP**: Liver Glucose Production
- **GA**: Glucose Absorption
- **GE**: Glucose Excretion
- **KIR**: Kidney Insulin Removal
- **PRIR**: Periphery Insulin Removal
- **LIR**: Liver Insulin Removal
- **IA**: Insulin Absorption
B.2 Model of Hovorka et al.

The model proposed by Hovorka et al. [6], [33] considers the plasma glucose, insulin (plasma and subcutaneous) and insulin action subsystems (Figure B.3). The glucose subsystem is represented with two-compartmental model, and includes renal glucose excretion, the endogenous glucose production, the insulin independent glucose flux, and the gut absorption dynamics. Insulin subsystem includes models for both plasma and subcutaneous insulin representation. Finally, the three-compartmental insulin action subsystem models the effect of insulin on glucose distribution/transport, glucose disposal, and endogenous glucose production.

Figure B.3. Compartmental diagram of glucose, insulin and insulin action subsystems [6].
Glucose Subsystem:

\[
\frac{dQ_1(t)}{dt} = - \left[ \frac{F_{c01}}{V_G G(t)} + x_1(t) \right] Q_1(t) + k_{12} Q_2(t) - F_R + U_G(t) + EGP_0 [1 - x_3(t)]
\]  
(B.34)

\[
\frac{dQ_2(t)}{dt} = x_1(t) Q_1(t) - [k_{12} + x_2(t)] Q_2(t)
\]  
(B.35)

\[
G(t) = \frac{Q_1(t)}{V_G}
\]  
(B.36)

Non-Insulin-Dependent Glucose Utilization:

\[
F_{c01}^e = \begin{cases} 
F_{01} & \text{if } G \geq 4.5 \text{mmolL}^{-1} \\
F_{01}G/4.5 & \text{otherwise}
\end{cases}
\]  
(B.37)

Renal Glucose Clearance:

\[
F_R = \begin{cases} 
0.003(G - 9)V_G & \text{if } G \geq 9 \text{mmolL}^{-1} \\
0 & \text{otherwise}
\end{cases}
\]  
(B.38)

Glucose Absorption from the Intestine:

\[
U_G(t) = \frac{D_G A_G t e^{-t/t_{max,G}}}{t_{max,G}^2}
\]  
(B.39)
Insulin Subsystem:

\[ \frac{dI(t)}{dt} = \frac{U_I(t)}{V_I} - \left[ k_e + k_{b1} + k_{b2} + k_{b3} \right] I(t) \] (B.40)

Subcutaneous Insulin Absorption:

\[ \frac{dS_1(t)}{dt} = u(t) - \frac{S_1(t)}{t_{max,I}} \] (B.41)

\[ \frac{dS_2(t)}{dt} = \frac{S_1(t)}{t_{max,I}} - \frac{S_2(t)}{t_{max,I}} \] (B.42)

\[ U_I(t) = \frac{S_2(t)}{t_{max,I}} \] (B.43)

Insulin Action Subsystem:

\[ \frac{dx_1(t)}{dt} = k_{b1} I(t) = k_{a1} x_1(t) \] (B.44)

\[ \frac{dx_2(t)}{dt} = k_{b2} I(t) = k_{a2} x_2(t) \] (B.45)

\[ \frac{dx_3(t)}{dt} = k_{b3} I(t) = k_{a3} x_3(t) \] (B.46)
Model Parameters:

Table B.4. Model Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{12}$</td>
<td>0.066 (min$^{-1}$)</td>
</tr>
<tr>
<td>$k_{a1}$</td>
<td>0.006 (min$^{-1}$)</td>
</tr>
<tr>
<td>$k_{a2}$</td>
<td>0.06 (min$^{-1}$)</td>
</tr>
<tr>
<td>$k_{a3}$</td>
<td>0.3 (min$^{-1}$)</td>
</tr>
<tr>
<td>$k_e$</td>
<td>0.138 (min$^{-1}$)</td>
</tr>
<tr>
<td>$V_I$</td>
<td>0.12 (L/kg)</td>
</tr>
<tr>
<td>$V_G$</td>
<td>0.16 (L/kg)</td>
</tr>
<tr>
<td>$A_G$</td>
<td>0.8 (unitless)</td>
</tr>
<tr>
<td>$t_{max,G}$</td>
<td>40 (min)</td>
</tr>
<tr>
<td>$t_{max,I}$</td>
<td>55 (min)</td>
</tr>
<tr>
<td>$F_{01}$</td>
<td>0.0097 (mmol kg$^{-1}$ min$^{-1}$)</td>
</tr>
<tr>
<td>$E GP_0$</td>
<td>0.0161 (mmol kg$^{-1}$ min$^{-1}$)</td>
</tr>
<tr>
<td>$S_{IT}$</td>
<td>$k_{b1}/k_{a1} = 51.2 \times 10^{-4}$ (min$^{-1}$ per mU L$^{-1}$)</td>
</tr>
<tr>
<td>$S_{ID}$</td>
<td>$k_{b2}/k_{a2} = 8.2 \times 10^{-4}$ (min$^{-1}$ per mU L$^{-1}$)</td>
</tr>
<tr>
<td>$S_{IE}$</td>
<td>$k_{b3}/k_{a3} = 520 \times 10^{-4}$ (per mU L$^{-1}$)</td>
</tr>
</tbody>
</table>
Nomenclature:

<table>
<thead>
<tr>
<th>Variables:</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>mass of glucose in the accessible compartment</td>
</tr>
<tr>
<td>Q2</td>
<td>mass of glucose in the non-accessible compartment</td>
</tr>
<tr>
<td>G</td>
<td>plasma glucose concentration</td>
</tr>
<tr>
<td>I</td>
<td>plasma insulin concentration</td>
</tr>
<tr>
<td>S1, S2</td>
<td>two-compartment chain representing absorption of subcutaneously administered short-acting</td>
</tr>
<tr>
<td>x1</td>
<td>remote effects of insulin on glucose distribution/transport</td>
</tr>
<tr>
<td>x2</td>
<td>remote effects of insulin on glucose disposal</td>
</tr>
<tr>
<td>x3</td>
<td>remote effects of insulin on endogenous glucose production</td>
</tr>
<tr>
<td>VG</td>
<td>distribution volume of the accessible compartment of glucose</td>
</tr>
<tr>
<td>VI</td>
<td>the distribution volume of insulin compartment</td>
</tr>
<tr>
<td>DG</td>
<td>amount of carbohydrates digested</td>
</tr>
<tr>
<td>AG</td>
<td>carbohydrate bioavailability</td>
</tr>
<tr>
<td>u(t)</td>
<td>insulin administration rate (bolus and infusion)</td>
</tr>
<tr>
<td>UI(t)</td>
<td>appearance rate of insulin in plasma</td>
</tr>
</tbody>
</table>


