COVER PAGE

DYNAMIC MODEL DEVELOPMENT AND RECEDING HORIZON CONTROL OF BLOOD GLUCOSE CONCENTRATION

BY

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TITLE PAGE

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DEPARTMENT OF CHEMICAL ENGINEERING,
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AHMADU BELLO UNIVERSITY, ZARIA
NIGERIA.

MARCH, 2018

DECLARATION

I Abdul-Alim Gambo IBRAHIM, hereby declare that this dissertation entitled "DYNAMIC MODEL DEVELOPMENT AND RECEDING HORIZON CONTROL OF BLOOD GLUCOSE CONCENTRATION" has been carried out by me in the Department of Chemical Engineering. The information derived from the literature has been duly acknowledged in the text and a list of references provided. To the best of my knowledge, no part of this project was previously presented for the award of degree or diploma at this or any other institution.

Abdul-Alim Gambo Ibrahim		
Name of Student	Signature	Date

CERTIFICATION

This is to certify that this dissertation entitled "DYNAMIC MODEL DEVELOPMENT AND RECEDING HORIZON CONTROL OF BLOOD GLUCOSE CONCENTRATION" by Abdul-Alim Gambo IBRAHIM with registration number P14EGCE8002 meets the regulations governing the award of Master of Science (M.Sc.) degree in Chemical Engineering of the Ahmadu Bello University, and is approved for its contribution to knowledge and literary presentation.

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DEDICATION

To the memory of my late mother **Hajiya Aminah Ibrahim.**

ABSTRACT

Biological systems usually consist of large number of components and involve processes at a variety of spatial, temporal and biological scales. This study presents a framework for model identification and the use of Global Sensitivity Analysis (GSA) in systems biology modelling and shows how the information content of clinical data from Short Insulin Tolerance Test (SITT) can be handled by optimal model-based estimation techniques. The goal is to identify dynamic model of type II diabetes and estimate a set of parameters of the model with greater accuracy and precision. Based on the SITT data, the blood glucose dynamic model was identified as a system of linear differential equation with constant coefficients (parameters). The sensitivity of the parameters was tested using a novel GSA based approach, and Derivative-Based Global Sensitivity Measures (DGSM). The proposed approach was implemented in SensSB (a Matlab based toolbox). For the purpose of comparison, the sensitivity of the model was also tested using Sobol's method and a local approach. The results have shown that the model is less sensitive to the third parameter (K_2) and the model fits the SITT data satisfactorily. Subsequently, a control strategy called receding horizon control was investigated to regulate blood glucose concentration under the model predictive control framework. Two forms of receding horizon control strategy (fixed-end and moving-end) were proposed and applied to the dynamic model to maintain blood glucose concentration. Different disturbance scenarios were generated to evaluate the performance of the two strategies in terms of its efficiency to handle disturbances. The control strategies successfully addressed the issues of the input/external disturbance considered for the patients in a virtual situations which maintain blood glucose level at 80.06 mg/dL.

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ABBREVIATIONS

NIDDM	Non-insulin dependent diabetes mellitus.
IDDM	Insulin dependent diabetes mellitus.
MM	Minimal model.
BGC	Blood glucose concentration.
PGL	Plasma glucose level.
MPC	Model predictive control.
RHC	Receding horizon control.
ANN	Artificial neural network.
NN	Neural network.
OGTT	Oral glucose tolerance test.
IVGTT	Intra-venous glucose tolerance test.
ITT	Insulin tolerance test.
SITT	Short insulin tolerance test.
FGB	Fasting blood glucose.
CMs	Compartment models.
GSA	Global sensitivity analysis
LSA	Local sensitivity analysis
DGSM	Derivate-Based Global Sensitivity Measures
HPA axis	Hypothalamic–pituitary–adrenal axis
HIEC	Health Innovation and Education Cluster
SRES	Stochastic Ranking Evolutionary Search

NOMENCLATURE

Symbol	Definition
G_1	Glucose concentration in the body.
G_2	Plasma blood glucose concentration.
G_o	Initial blood glucose concentration during the fasting period.
K_1	Rate of glucose absorption.
K_1	Rate of disappearance of glucose.
T	time
N	prediction period.
x	Current state vector.
u	Control variable of the system.
l	State vector.
ψ	Output equations.
N_y	Prediction horizons.
N_u	Control horizons.
Q	Deviation weights.
R	Control variable from the set points, and finally
k	time step.

CHAPTER ONE
INTRODUCTION

1.1 BACKGROUND OF THE STUDY

At the boundary between biological sciences and engineering disciplines, there is an interesting set of problems mostly classified as bio-systems. Further subdivision of these systems yield areas addressing biomedical and biotechnical issues. While biomedical deals with human and medicine, biotechnical issues are non-human related (Ramprasad, 2004). These bio-systems offer a challenging set of modelling and regulation problems to the biological, medical and engineering communities. The biomedical problem of glucose control using different control strategies in diabetes patients is the focus of this study.

Diabetes is a disease characterized by inadequate control of blood glucose concentration in the body (Cescon, 2013). Normally, the control of blood glucose concentration relies on two hormones produced in the pancreas, insulin and glucagon, both of which indirectly affect the blood glucose concentration; while insulin lowers it glucagon increases it. The food intake in the body results in an increase in the glucose concentration that stimulates the β-cells of the pancreas to produce insulin, which prevents the glucose concentration from increasing substantially (Cescon, 2013).

The prevalence of diabetes in the world is growing at an unprecedented rate and has become a health concern. The International Diabetes Federation states that “diabetes currently affects more than 300 million people in the world. This represents 6% of the world's adult population and every ten seconds, two people are diagnosed with diabetes somewhere in this world” (World Health Organization, 2016).

Diabetes mellitus is of three types: type I, type II and type III. Type I diabetes mellitus are called juvenile diabetes or Insulin Dependent Diabetes Mellitus (IDDM) and is

usually diagnosed in children, teenagers, or young adults. In type I diabetic, the glucose concentration is elevated beyond the normoglycemic range (70-100 mg/dL) due to the insufficient insulin secretion from the β-cells of islets of Langerhans present in the pancreas (Ramprasad, 2004). Type II diabetes mellitus are called adult-onset diabetes or Non-Insulin Dependent Diabetes Mellitus (NIDDM), is the most common form of diabetes. People can develop type II diabetes at any age, even during childhood. This form of diabetes usually begins with insulin resistance, a condition in which fat, muscle and liver cells do not use insulin properly (Ramprasad, 2004). The third type of diabetes mellitus called gestational diabetes, is a temporary condition that occurs during pregnancy. It affects approximately two to four per cent of all pregnancies and involves an increased risk of developing diabetes for both mother and child.

In a normal healthy person, the natural internal control of blood glucose concentration is accomplished by a feedback control mechanism. In type I diabetes, this mechanism must be employed by an external artificial control mechanism that controls the injection of the insulin with respect to the present blood glucose concentration which must be precise and relatively high performance (Ibrahim *et al.,* 2016). Hence, to overcome this problem, several researches from many disciplines as well as control engineering have participated in this commitment to model the control systems.

Diabetes mellitus type II (also known as type II diabetes) is a metabolic disorder characterized by impaired insulin secretion or action, leading to a condition where an individual rely on frequent injections of exogenous insulin to survive. The amount injected will affect the quality of the blood glucose regulation. Insufficient supply of insulin may lead to periods of high blood glucose (hyperglycemia), which may lead to long-term

complications, such as blindness, nerve disease or kidney disease. On the other hand, injecting the insulin more than the required amount may lead to low blood glucose (hypoglycaemia), which has immediate effects, such as seizures or even death (Boiroux, 2012). Therefore accurate insulin dose is required to maintain the blood glucose concentration at the desired value.

Insulin can be injected with an insulin pen or an insulin pump (Naerum, 2010). The insulin pen is typically used for injecting insulin boluses at meal times, while the insulin pump is used for injecting insulin almost continually with an injection, e.g., every 5 minutes (Hirst, 1993). The glucose concentration can be measured with a continuous glucose monitor. These measurements can be used by a control algorithm to calculate how much insulin should be pumped at the current time measure. This calculation can be done using Model Predictive Control (MPC) also known as Receding Horizon Control (RHC).

RHC is a nonlinear control policy that handles input constraints, output constraints, and various control objectives. Using RHC, a system can be controlled near its physical limits, often obtaining performance superior to linear control. RHC uses the current glucose concentration and meal input to predict future glucose concentrations (Zhou *et al.,* 2010). Typically, predictions are made with a linear model. If a high glucose concentration is predicted, more insulin is injected early enough to decrease the glucose concentration to a proper value at the predicted time. RHC predicts the glucose concentration using the insulin infusion rate from only the current time sample. The optimal insulin infusion rate should then be found to get the best possible predictions.

The MPC algorithm is made up of two elements: a prediction model of the system and the optimization tool. The set of future decisions are computed by the optimization tool

according to the constraints, cost function, and prediction horizon. The optimization problem is solved over the prediction horizon where a sequence of decision variables are determined for a number of time steps and then implementing only the first step in the series. The time then moves by one step with the information from the preceding time step used as input and the process is repeated until the last step. The difference between two time steps is determined by the recommended sampling time.

The use of receding horizon approach under the model predictive control (MPC) framework is a good option. All MPC algorithms share common elements, and different options can be selected for these elements. These elements are the prediction model, objective function and calculation of the control law. Based on the prediction horizon length, receding horizon strategy can be fixed-end (where the prediction length is varying) or moving-end (in which the length is constant).

1.2 PROBLEM STATEMENT

Blood glucose regulation is now an issue that can be addressed by employing control algorithm that uses the previous and current state measurements of blood glucose concentration to predict the future glucose concentration level and hence compute the actual amount of insulin required.

Despite the usefulness of the model based algorithms in controlling blood glucose level, state-space models following short insulin tolerance test for diabetics has never been reported in the literature. Moreover, fixed-end receding horizon control has not yet been exploited in research studies involving blood glucose regulation.

1.3 AIM AND OBJECTIVES

The aim of this work is to identify and develop a dynamic model with the view to synthesizing a controller for prediction and control of blood glucose concentration.

The specific objectives includes:

1. To model the interaction between glucose and insulin in blood following the short insulin tolerance test by using system identification techniques.
2. To develop effective control strategies under the model predictive control framework for regulating blood glucose concentration.
3. To compare the control strategies in terms of performance for recommendation on the best control structure to adopt for type II diabetic patients.

1.4 SCOPE OF THE WORK

This work was limited to:

1. Dynamic model development of blood glucose concentration from short insulin tolerance test data.
2. Parameter estimation and global sensitivity analysis using SensSB software toolbox in MATLAB.
3. Development of a controller from the developed model using fixed and moving end receding horizon control strategies for blood glucose regulation.

1.5 RESEARCH JUSTIFICATION

1. Glucose metabolism in diabetic patient will be modelled without causing serious and irreversible harm to the subject.
2. A model based controller that can be very helpful in understanding the pathophysiology of the disease.
3. The result of this study will provide a mathematical model which should be considered as a useful resource for clinical investigations.

CHAPTER TWO
LITERATURE REVIEW

2.1 PREVALENCE OF DIABETES IN NIGERIA

The prevalence of diabetes mellitus in Nigeria has increased from 2.2% as reported by Akinkugbe (1997) from a national survey to 5.0% by 2013 estimates of the International Diabetes Federation (IDF) (Oputa, 2013). The prevalence of the varying types of diabetes mellitus is increasing globally, including in Nigeria. Type II diabetes mellitus is increasing in adolescents, and gestational diabetes mellitus (GDM) is also more recognized now. Type I diabetes mellitus is often misdiagnosed or undiagnosed and may result in coma and death.

The progressive increase in the prevalence rate of diabetes mellitus is associated with lifestyle changes, overweight and obesity, physical inactivity, alcohol consumption, dietary changes and cigarette smoking- factors that are potentially modifiable (Ejike *et al.,* 2015). So much attention is being given even recently to communicable diseases like the Human Immunodeficiency Virus (HIV), tuberculosis, and malaria at the detriment of the emerging epidemic of non-communicable diseases like diabetes mellitus, hypertension and heart disease. Over 30% of our elite population including decision-makers are diabetic. More painfully so, the majority of the Nigerian diabetic population cannot afford meaningful treatment, and over 80% of the healthy population are ignorant about diabetes mellitus (Chinenye *et al.,* 2012).

There is a need for more sponsored independent studies on prevalence and incidence rates around the different states of the federation or geopolitical zones in collaboration with the Federal Ministry of Health, to ensure proper documentation for future references and to provide proper policy framework and guidelines for legislators.

In some parts of Nigeria, some health care professionals still advice persons living with diabetes not to eat much carbohydrate but only proteins when current research findings advocate use of complex carbohydrates and other food groups in moderate quantity. The Federal Government of Nigeria through the Federal Ministry of Health needs to quickly act through the Diabetes Association of Nigeria which have chapters in many states of the federation, and other stakeholder's associations and non-governmental organizations to ensure uniformity of standards of care and preventions (Chinenye *et al.,* 2012).

2.2 BLOOD GLUCOSE-INSULIN SYSTEM

The glucose-insulin system is an example of a closed-loop physiological system. A healthy person normally has a blood glucose concentration at about 70−110 mg/dL. The glucose-insulin system helps us to keep this steady state. In Figure 2.1 a simple description of the system is shown. Most of the time a healthy person is in the green area, having normal blood glucose concentration.

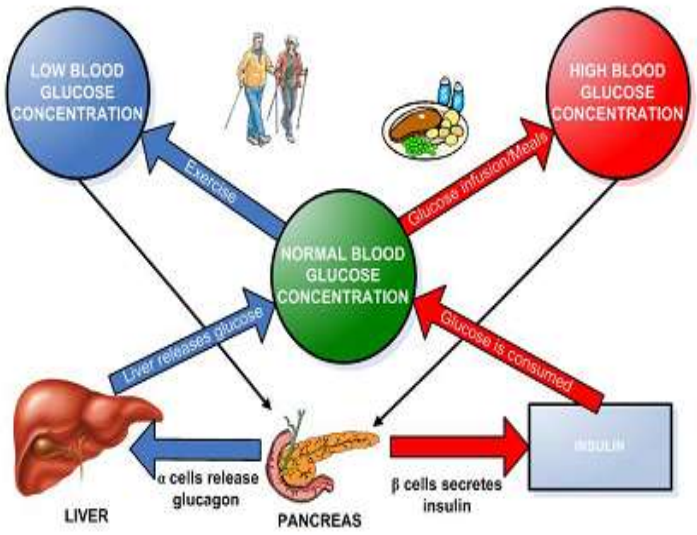


Figure 2.1 The blood glucose-insulin system (Friis-jensen, 2007)

If the person then ingest additional glucose to the system e.g. via a meal, the person moves to the red area, with a higher blood glucose concentration. When this happens

a signal is sent to the pancreas, in which β cells react by secreting the hormone insulin. This insulin increases the uptake of glucose by the cells, liver etc. and brings the person back to the green area. If the blood glucose concentration goes below the normal level, the person is in the blue area. This could happen as a response to exercise, which increase the glucose uptake (Friis-jensen, 2007). When the person is in the blue area with low blood glucose concentration a signal is also sent to the pancreas. The pancreas α cells react by releasing glucagon. This glucagon affects the liver cells to release glucose into the blood until the person is back in the green area again (Makroglou *et al.,* 2006). This is a very simple description of a more complicated system.

2.3 BLOOD GLUCOSE TEST

Diabetes and other diseases caused by malfunctions in the glucose-insulin system are one of the reasons that many mathematical models have been made over time to describe this dynamical system (De Gaetano and Arino, 2000). These mathematical models are based on and used to explain the tests. The models and tests can help to improve the situation for many people suffering from diabetes.

2.3.1 The Oral Glucose Tolerance Test (OGTT)

One of the tests used is the Oral Glucose Tolerance Test (OGTT). In this test the subject fast for an 8-hour period after which the blood glucose and insulin concentrations are measured (Bergman, 1997). Then the subject ingest glucose in a liquid solution orally. After this ingestion, new measurements are taken over a two-hour period. The blood glucose concentration level is described in Table 2.1 and a graphical representation of these limits can be seen in Figure 2.2. The green graph indicate normal glucose tolerance, yellow graph is a pre-diabetes state and red graph shows diabetes state.

Table 2.1: Blood glucose level for an oral glucose tolerance test (OGTT) (Friis-jensen, 2007)

Blood glucose level	**State of diabetes**
Less than 140 mg/dL	Normal glucose tolerance
From 140 to 200 mg/dL	Pre-diabetes
More than 200 mg /dL	Diabetes

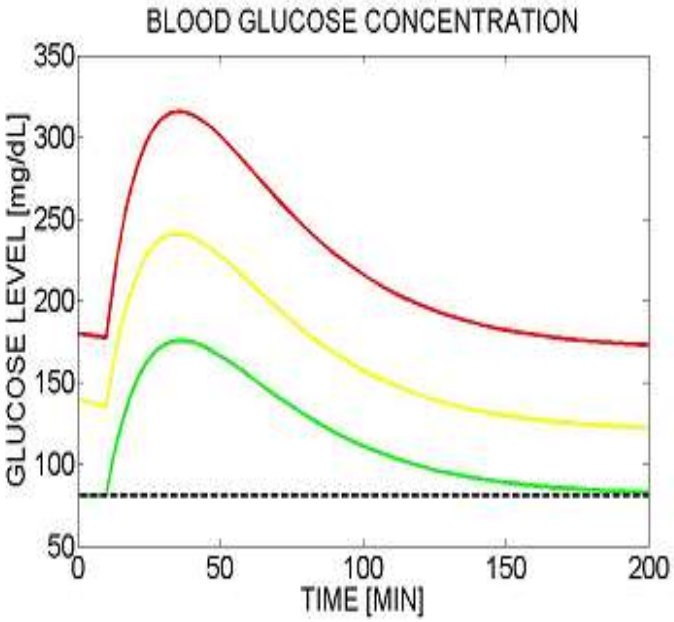


Figure 2.2: The pattern of an OGTT.

2.3.2 The Intravenous Glucose Tolerance Test (IVGTT)

Another test is the Intravenous Glucose Tolerance Test (IVGTT). Together with a mathematical model, this test can be used to estimate Insulin Sensitivity (IS), glucose effectiveness (SG), and the pancreatic responsiveness parameters $\varphi 1$ and $\varphi 2$ in a subject (Pacinic and Bergman, 1986).The IVGTT test procedure begins with an injection of a glucose bolus intravenously, containing 0.30 g glucose per kg body weight. Then you take blood samples frequently for a 3-hour period. These blood samples are analyzed and glucose and insulin levels are measured. A typical IVGTT for a normal subject, from studies by

Pacinic and Bergman (1986) is shown in Figure 2.3. As you can see the glucose level decays slowly to a minimum level below the basal value and then slowly reaches the basal value. The insulin peaks just after the injection, and then decays to a level above the baseline and then peaks a little again. Finally, it decays to the basal value. This is just a typical pattern and the glucose and insulin level may not behave exactly like this.

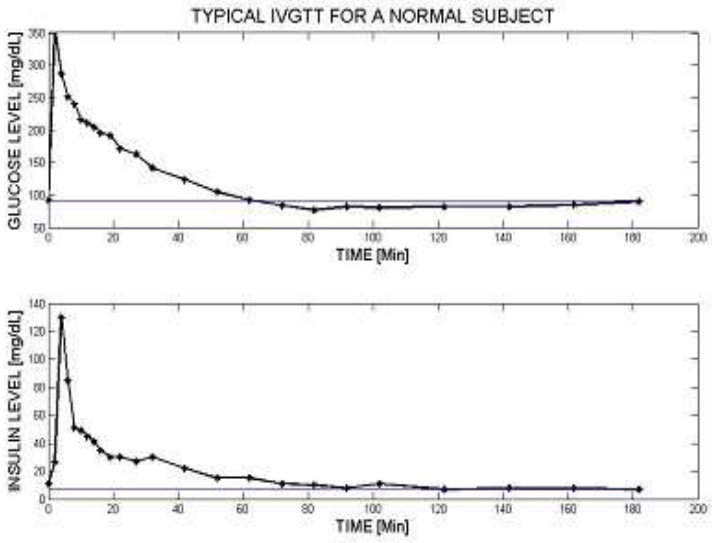


Figure 2.3: An IVGTT for a normal subject.

2.3.3 Fasting Blood Glucose

A third test and much easier test is the fasting blood glucose. Here the subject/patient has to fast for a period of 8-10 hours, then a measurement of the glucose is made (Friis-jensen, 2007). The test results can be interpreted as shown in Table 2.2:

Table 2.2: Blood glucose level for fasting blood glucose test (Friis-jensen, 2007)

Blood glucose level	**State of diabetes**
From 70 to 99 mg/dL	Normal glucose tolerance
From 100 to 125 mg/dL	Pre-diabetes
More than 126 mg/dL	Diabetes

2.3.4 Insulin Tolerance Test (ITT)

The insulin tolerance test (ITT) is widely regarded as the gold standard for testing for adrenal insufficiency. It is particularly useful for detecting secondary adrenal insufficiency. Intravenous insulin is administered (0.1 units/kg) with the intention of inducing hypoglycemia (Carmichael, 2011). Symptomatic hypoglycemia, with blood glucose values below 40 mg/dL, is required to evoke a reliable central stress response with activation of the HPA axis. Higher doses may be required in patients with insulin resistance or acromegaly (Carmichael, 2011).

The test is usually contraindicated in patients older than 60 years and in those with risk of seizures, or suspicion or history of active cardiovascular disease. Accordingly, the procedure requires close supervision throughout the duration of testing and should be performed in specialized centers with precautions to avoid consequences of potential adrenal crisis. Measurements are obtained at 0, 30, and 60 minutes with serum cortisol levels greater than 18 ng/mL indicating a normal response. The test is not frequently performed, but remains a valuable tool in the assessment of adrenal insufficiency, especially following recent pituitary surgery (Carmichael, 2011).

The advantages of the ITT include its simplicity, rapidity and the use of a bolus injection of insulin. The bolus injection of insulin mimics the physiological pulsatile release of insulin (Prksen *et al.,* 1996). Furthermore, because glucose tolerance after a meal is dependent on insulin sensitivity, measuring insulin sensitivity in the prandial state is physiologically relevant.

Some of the drawbacks of this method include the supraphysiological insulin dose used, and also the fact that the test does not differentiate peripheral versus hepatic insulin resistance (Hirst *et al.,*1993). Another major limitation of this test is the risk of

hypoglycemia. Hypoglycemia triggers hormonal responses, which may interfere with insulin sensitivity and in turn slows the disappearance rate of glucose from plasma (Reaven, 1983). In this view, the fall in plasma glucose concentration would be a function of the interplay between insulin, on the one hand, and glucagon, catecholamines, growth hormone and cortisol, on the other. Given that, the counter-regulatory response occurs only 15–20 min after insulin injection. The glucose falls occurring in the first 15 min after intravenous insulin administration is probably a function of insulin-stimulated glucose uptake by tissues as well as insulin ability to suppress glucose output by the liver (Akinmokun *et al.,* 1992).

A lower insulin dose method of 0.05 IU/kg body weight, or shortening the test to 15 min was suggested as an attempt to decrease the risk of hypoglycemia (Chen *et al.,* 1998; Hirst *et al.,* 1993). The shorter version reported by Bonora *et al.,* (1989) and Akinmokun *et al.,* (1992) derived from the notion that the counter-regulatory hormone response occurs only after 20 min of the insulin infusion (Monzillo and Hamdy, 2003). The ITT has been shown to correlate with the Health Innovation and Education Cluster (HIEC) in several studies (Akinmokun *et al.,* 1992). However, arterialization of blood is essential in the ITT, as data from standard venous blood measurements showed no significant relationship with HIEC-derived glucose disposal (Akinmokun *et al.,* 1992).

In conclusion, the ITT should be used with great caution in insulin sensitive individuals because of the increased risk of hypoglycemia, even when the smaller dose version of the test is used. The shorter ITT is a valid test in large-scale studies, especially when the site of resistance is not of importance.

2.3.5 Short Insulin Tolerance Test (SITT)

The SITT measures the decline in serum glucose after an intravenous bolus of regular insulin (0.1-0.5u/kg) is administered. Which is the simplified version of ITT.

Several insulin and glucose levels are sampled over the following 15 minutes (depending on the protocol used). SITT primarily measures insulin-stimulated uptake of glucose into skeletal muscle. Because the test is so brief, there is very little danger of counter-regulatory hormones interfering with its regulatory action. The glucose disappearance rate constant 'K' is determined using the $t/_2$ derived from the slope of the graph of the glucose disappearance rate, the graph being drawn by the line of best fit from the least squares method of regression (Fasanmade, 1987).

2.4 MODELING BLOOD GLUCOSE DYNAMICS

Modeling glucose-insulin interaction in the human body has been an active research area for decades (Lin, 2011). In this section, a brief review of numerous models proposed in the literature is provided, by classifying them into two groups:

1. Physiological models, and
2. 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 (Lin, 2011). These models also include pharmacokinetic diagrams of exogenously administered insulin and glucose absorption from the gastrointestinal tract

following a meal consumption. Since blood glucose regulation is a highly nonlinear and complex process, most of the physiological models are general representation of an average subject under specific and disturbance-free conditions, and they are typically nonlinear with too many parameters to be identified for individualized needs (Lehmann and Deutsch, 1992).

The most extensively studied physiological model in the literature that describes glucose-insulin interactions in the human body is the so-called Minimal Model (MM) (Bergman and Lovejoy, 1997). 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 (Bergman and Lovejoy, 1997). Plasma glucose dynamics, plasma insulin dynamics, and insulin concentration in a remote inaccessible compartment are included in the model. Stability problems of the MM have been revealed by De Gaetano and Arino (2000), the authors showed that the MM does not admit equilibrium and the insulin concentration in the remote compartment increases without bounds for some situations.

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 behaviour (Florian, 2005).

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 (Lin, 2011). Tresp *et al.,* (1999) developed neural network (NN) models for blood glucose metabolism. They compared 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 Self-Monitoring of Blood Glucose (SMBG) measurements of a male patient with type I diabetes over a period of 63 days.

Promising results were reported in terms of prediction accuracy. Empirical Volterra series models of glucose-insulin dynamics have been developed by Florian (2005). 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 Marmarelis (2007) developed Volterra-type models from input-output data generated by a simulation study. Minimal model was 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 were employed. Iterative gradient descent scheme utilized for LVN training. Results demonstrate the feasibility of obtaining data-

driven nonparametric models. The authors also demonstrate that data-driven models are more responsive to adaptive and patient-specific estimation compared to physiological models.

This study is focused on the model identification of type II diabetes and sensitivity analysis on the set of parameters of the model with greater accuracy and precision based on SITT data

2.5 BLOOD GLUCOSE REGULATION

Several control algorithms were developed and studied for different models of diabetic in the literature. These were comprehensively reviewed by Parker *et al.,* (1999) and Peppas (2001). The earliest diabetes regulation work dates to the "BIOSTATOR" algorithm and device of Clemens *et al.,* (1979). This feedback controller utilized a low volume continuous flow blood glucose sampling mechanism with a dual infusion system (insulin and dextrose) to maintain blood glucose concentration at a user-defined value. The multi-channel nature of the algorithm could lead to interactions such as an increase in glucose stimulating the insulin release from its reservoir leading to lowering of glucose level which stimulates the dextrose release from its reservoir and continuation of this cycle. This system requires implantation of two reservoirs and is difficult due to additional size of the second depot and patient-specific requiring individualization prior to implementation. Sorensen (2008) tested an Internal Model Control (IMC) strategy on his model for a particular set of patient parameters.

Optimal control theory was applied to the minimal model of Bergman *et al.,* (1987) in two different studies (Fisher, 1991; Ollerton, 2007). Ollerton (2007) used an integral squared error cost function based on deviation from the desired glucose value. Sampling

times of 10 and 180 min were studied. The longer sampling time had a longer rise time and was less sensitive to noise about the basal state, but could miss significant disturbances which occurred in the inter-sample window. With sampling time of 10 min, the controller was sensitive to oscillations of the glucose profiles about the basal state and resulted in physiologically unrealistic insulin profiles characterized by high amplitude sustained oscillations (ringing). An insensitive model was introduced by Ollerton (2007), most likely based on a type of dead-band control, but no method for development of the insensitive model was discussed.

Fisher (1991) applied optimal control theory to "minimal" model by using integral squared error (ISE) based objective function. He reported that the deviations in the glucose concentration from the set point were minimized. The study examined three insulin infusion profiles, determining that an initial injection plus optimal hourly infusion minimizes the cost function for an initially hyperglycemic patient. This control design also suffered from long sampling time (180 min) problem of missing fast or inter-sample distribution and was not robust to patient uncertainty, as in Ollerton (2007).

Proportional-Derivative (PD) and Proportional Integral (PI) type controllers (belonging to the Proportional-Integral-Derivative (PID) controller family) were employed by Fischer (1990) and Chee *et al.,* (2003) respectively for blood glucose control. Chee *et al.,* (2003) have developed a PI controller to specify the amount of insulin to be injected based on glucose measurement in a real-time manner by continuous glucose monitoring system (CGMS). This closed-loop control was clinically tested on five patients and was able to control only one patient's glycemia without manual intervention. Even though manual intervention is due to the real-time sensor reading, refinement of the algorithm and sensor

accuracy are needed.

Parker *et al.,* (1999) have done an extensive study on blood glucose control and compared the performance of several model predictive controllers such as discrete internal model control (IMC), model predictive controller (MPC), model predictive controller with State Estimation (MPCSE), and nonlinear quadratic dynamic matrix control with state estimation (NLQDMCSE). Cammelia *et al.,* (2001) used IMC framework to maintain the blood glucose concentration in diabetics simulated by Bergman (1997) and automated insulin dosage advisor (AIDA) of Lehmann and Deutsch (1992) models. In the synthesis and/or evaluation of these controllers, however, the inherent uncertainty in the model has not been addressed. Such control strategies could lead to significant performance degradation in the presence of inevitable patient-model mismatch.

Moreover, Femat (2004) have addressed blood glucose control for diabetics as a set point tracking problem using H∞ controller strategy. In this study, blood glucose regulation problem was reformulated as a tracking problem. The amount of insulin to be injected was specified by H∞ controller strategy to track the glucose profile of the healthy patient subjected to meal disturbances. Even though maximum tracking error for nominal and worst case condition reported are 15 mg/dL, there is a possibility for prevalence of hyperglycemia for quite some time, which could result in retinopathy and nephropathy over a long run.

2.6 SENSITIVITY ANALYSIS

Sensitivity analysis (SA) generally is the study of how the uncertainty in the output of a mathematical model or system can be apportioned to different sources of uncertainty in its inputs (Pannell, 1997). The SA methods are used to determine the influence of uncertainty factors in the output of a model, They also indicates which of the uncertainty factors need to

be further examined in order to reduce uncertainty (Saltelli, 2006).

It is highly recommended as part of the models quality control to use SA techniques which improves model's perception and provide useful information regarding the real system (Hu and Shi, 2010). Sensitivity analysis method is classified into local methods (LSA) and Global methods.

2.6.1 Local Sensitivity Analysis

Local sensitivity analysis methods evaluate sensitivity of parameters in a restricted location, and they are mainly used for a rough and preliminary assessment of the model's output. They calculate the gradient of the response with regard to its parameters around a nominal value (Sudret, 2007). However, it is highly likely that these methods will result in a less informative outcome concerning the importance of the examined parameters, especially when they deal with a variety of different parameters, varying concurrently (Hu and Shi, 2010).

2.6.2 Global Sensitivity Analysis

Global sensitivity analysis (GSA) methods, unlike local sensitivity methods, take into account a specific, but reasonable and predefined region for the parameters domain. Thus, they provide quantitatively the action patterns of the parameters on the model's prediction (Hu and Shi, 2010). Techniques of global sensitivity analysis appear more appealing due to the fact that they investigate the entire range of parametric uncertainty and, despite the complexity of the model, interactions of parameters are also considered and estimated by changing them simultaneously, while there is no need for a nominal value to be set (Saltelli, 2006). Hence, they provide a wider range of information than local sensitivity methods that do not exhibit the same explorative behaviour (Frey and Patil, 2002). One of the most advantageous characteristics of global sensitivity methods is that they are

independent of characteristics of the model such as linearity and monotonicity between inputs and outputs (Buis *et al.,* 2010).

2.7 RECEDING HORIZON CONTROL

Receding horizon control (RHC), otherwise known as model predictive control (MPC) (Goodwin, 2005; Kwon, 2005; Maciejowski, 2003) is a type of feedback control mechanism that was popular in early 1980s. With RHC, an optimization problem is solved at each time step to determine a plan of action over a fixed time horizon, then the first input is applied from the plan. The planning process is repeated to solve a new optimization problem at the next time step, with the time horizon shifted one step forward (Mattingley and Boyd, 2010).

RHC is a nonlinear control policy that handles input/output constraints, and different control objectives. In RHC, dynamic systems can be controlled close to their physical limits, obtaining performance superior to linear control (Mattingley and Boyd, 2010). RHC methods found its application in process industry particularly in oil refineries and chemical plants (Diamanti, 2016), they are also used progressively in other areas, such as cement industry, robotic science, and fields of biomedical engineering in clinical anesthesia and diabetes among others (Camacho and Bordons, 2004). The success and efficient performance of RHC techniques achieved in all these diverse scientific fields indicates that RHC methodologies are able to control a wide range of systems with great accuracy, for long periods of time (Diamanti, 2016).

2.7.1 Receding Horizon Control Strategy

Fisher (1991) and Ollerton (2007) used optimal control theory to find the values of input variables u that optimize a cost function J. The change in x was determined by the

influence of u on J (Grema and Cao, 2015; Hamisu *et al.,* 2014). The optimal control algorithm developed for linear and nonlinear systems is an extension of RHC as reported in Kowalska and Mohrenschildt (2011), where a fixed horizon optimization problem is solved in a sequence of predicted inputs and a prediction horizon is determine by implementation of the first step in the series. The process is repeated by moving one step forward to obtain the prediction time (Goodwin *et al.,* 2006).

The methods of RHC is defined by Kwon and Han, (2005) as follows: "At the current time, the optimal control is obtained, either closed-loop type, or open-loop type on a finite fixed horizon from the current time k, say [k, k + N]. Among the optimal controls on the entire fixed horizon [k, k + N], only the first one is adopted as the current control law. The procedure is then repeated at the next time say, [k +1, k+1+N]", (Grema and Cao, 2015).

A typical RHC optimization problem is formed as follow (Efstratios, 2012):

$$\min_{u(0),\ldots u(N)} J = \sum_{k=0}^{N_y} y'(k)Qy(k) + \sum_{k=0}^{N_u} u'(k)Ru(k)$$

Subject to $x(k+1) = l(x(k), u(k))$

$$y(k) = \psi(x(k), u(k))$$

$$x_{\min} \le x(k+1) \le x_{\max}, \qquad k = 0,1,\ldots N_y$$

$$u_{\min} \le u(k+1) \le u_{\max}, \qquad k = 0,1,\ldots N_u \qquad 2.1$$

Where:

N = prediction period.

x = current state vector.

u = control variable of the system.

l = state vector.

ψ = output equations.

N_y = prediction horizons.

N_u = control horizons.

Q = deviation weights.

R = control variable from the set points, and finally

k = is the time step.

The concepts of RHC strategy is shown in Figure (2.4), where the sequence of control action is obtained by solving an objective function over a finite time horizon (Diamanti, 2016). The main advantage of RHC strategy is that it is a model based, hence, physical and operational constraints on state and control variables can be easily handled. It also has the advantage of taking into consideration of these constraints to calculate the future control action for being an online optimization methods (Dua *et al.,* 2008).

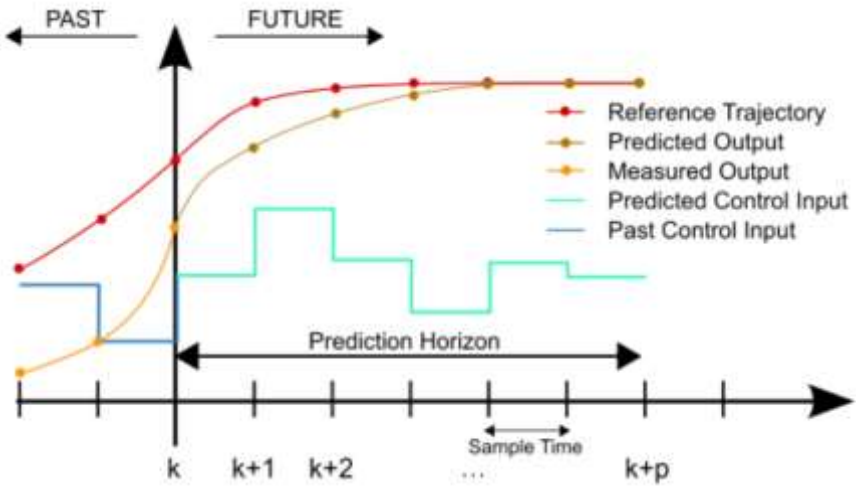


Figure 2.4: Model predictive control implementation (Efstratios, 2009).

The strategies of RHC with respect to the prediction horizon are of two types namely;

fixed and moving end control strategies. In fixed end RHC, the prediction time equals the entire control period which decreases subsequently as the control advances, while in moving end control strategy, the length of the prediction time remains constant (Grema, 2015; Hamisu, 2014). See Figures 2.5 and 2.6.

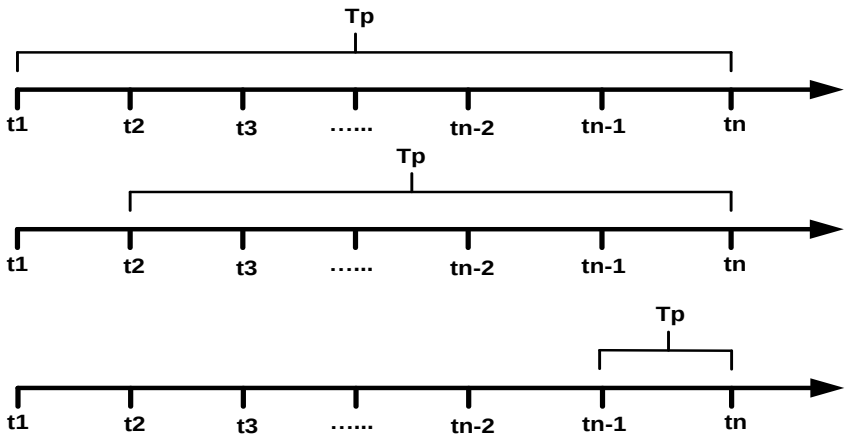


Figure 2.5: Fixed end receding horizon (Grema, 2015; Hamisu, 2014)

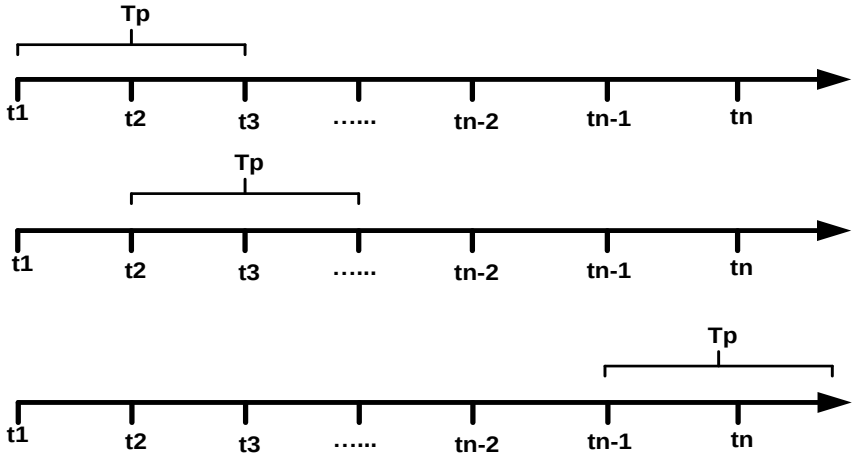


Figure 2.6: Moving end receding horizon (Grema, 2015; Hamisu, 2014)

In this work, blood glucose control is solved over the fixed end and moving end receding horizon strategies. The key advantage of the strategies is that they accommodate new information or uncertain parameters (disturbance) such as too much food, like a meal or snack with more carbohydrates than usual, stress which can produce hormones that raise blood glucose levels or too much insulin or oral diabetes medications within the scheduling

horizon. Fixed end receding horizon control was compared with a moving end receding horizon control strategies and also some disturbance scenarios were introduced to evaluate the performance of both strategies for recommendation to medical and clinical professionals.

2.7.2 Receding Horizon Control of Blood Glucose Concentration

Model based controllers have wide range of applications in biomedical engineering, more specifically in control of blood glucose concentration for patients suffering from diabetes mellitus (Peppas, 2001), control and delivery of electrical signals in case of Parkinson's disease and control of mean arterial pressure under anesthesia (Doyle *et al.,* 2011).

Model predictive control rises as an extremely promising technology in the area of artificial pancreas research (Peppas, 2001). The term artificial pancreas was explained formerly by Diamanti (2016) as the closed-loop control of the physical regulatory system of a patient with type I diabetes mellitus with complete deficiency of produced insulin. Most importantly, this method deals naturally with constraints, therefore, it guarantees patient's security (Cobelli *et al.,* 2011).

CHAPTER THREE
MATERIALS AND METHODS

3.1 INTRODUCTION

This chapter described the methods and procedure followed in achieving the results presented. The study begins with dynamic model development for blood glucose concentration from short insulin tolerance test data obtained by Gutti *et al.,* (2010). Subsequently, a global sensitivity analysis was conducted with the use of SensSB software toolbox in MATLAB to identify the most sensitive parameter of the model to the glucose response. Finally, a receding horizon control strategies was introduced in order to regulate the blood glucose concentration.

3.2 MATERIALS AND EQUIPMENT

3.2.1 System Specification

Windows: Windows 10 Home

Processor: AMD A4-500 APU with Radeon (TM) HD Graphics 1.5GHz

RAM: 4.00GB

Hard Disk: 500GB

System Type: 64-bit operating system, x64-based processor

3.2.2 MATLAB Specification

R2016a (9.0.0.341360)

64-bit (win64)

License number: 123456

Solver: ode45

Toolbox: SensSB Toolbox, MPC Designer, System Identification.

3.3 METHODS

3.3.1 Data Acquisition

The Short insulin Tolerance Test (SITT) data was conducted at the General Out-Patients Department (GOPD) of University of Lagos Teaching Hospital by Fasanmade (1987), the data was obtained by Gutti *et al.,* (2010), adhering strictly to regulation for use of human subjects. Unlike in Gutti *et al.,* (2010), here, the data was classified into parameters and control variables and stored in matrix G with the amount of insulin injected as input variable (manipulated variable). Refer to Appendix A for the SITT data.

3.3.2 Blood Glucose Concentration Model Development

The interaction of blood glucose concentration in human body can be formulated based on the law of conservation of mass as follows:

$$\text{Rate change} = \text{in} - \text{out} \tag{3.1}$$

From Equation (3.1), the rate change of glucose concentration can be written as

$$\text{Rate change of glucose concentration} = \text{Glucose}_{\text{in}} - \text{Glucose}_{\text{out}} \tag{3.2}$$

The rate change of glucose concentration is determined by insulin independent glucose uptake in which the SITT was conducted on patients with non-insulin dependent diabetes mellitus within the age range of 25-60 years as reported in Gutti *et al.,* (2010).

Let G_1 denote the amount of glucose concentration in the body and G_2 denotes the blood glucose concentration at time $t \geq 0$. From the information available, assuming the reaction kinetics follows first order, Equation (3.2) can be mathematically written as:

$$\frac{dG_1}{dt} = -k_1 G_1 \tag{3.3}$$

$$\frac{dG_2}{dt} = k_1 G_1 - k_2 \left(G_2 - G_0\right) \tag{3.4}$$

Where G_1 (mg/dL) is the glucose concentration in the body, G_2 (mg/dL) is the plasma blood glucose concentration, G_0 is the initial blood glucose concentration during the fasting period (baseline value) at $t=0$. The initial condition are $G_1(0)=G_0$ and $G_2(0)=G_0$, the rate constant $k_1(\min^{-1})$ is the rate of glucose absorption and $k_2(\min^{-1})$ is the rate of disappearance of glucose and *t* is the time taken during the experiment (min). Equation (3.3) and (3.4) represent the glucose-insulin system following the short insulin tolerance test (SITT). Note that in Equation (3.3), the short insulin tolerance test was done at a fasting level, therefore there has been no flow of glucose into the body.

3.3.3 Mathematical Formulation

In order to determine the blood glucose concentration level $G_2(t)$ explicitly, the differential Equations (3.3) was solved, and expression for $G_1(t)$ was obtained. After, the variables in Equation (3.3) was separated which gives the following,

$$\int \frac{dG_1}{G_1} = \int -K_1 dt \Rightarrow \ln|G_1| = -K_1 t + d$$

$$G_1(t) = G_0 e^{-K_1 t} \tag{3.5}$$

Note that the Equation (3.5) is a first order linear differential equation of the form:

$$\frac{dy(t)}{dt} + p(t)y(t) = q(t) \tag{3.6}$$

It has been verified in Ganesh (2009) that:

$$y = e^{-\int p(t)dt}\left[\int q(t)e^{\int p(t)dt}dt + C\right] \tag{3.7}$$

Equation (3.7) represent the solution to Equation (3.6) where C is the constant, substituting Equation (3.5) into Equation (3.4) gives a linear first order differential equation:

$$\frac{dG_2(t)}{dt} + K_2 G_2(t) = K_1\left(G_0 e^{-K_1 t}\right) + K_2 G_0 \qquad 3.8$$

Equation (3.6) has the following form of solution:

$$G_2(t) = e^{-\int K_2 dt}\left[\int \left(K_1 G_0 e^{-K_1 t} + K_2 G_0\right) e^{\int K_2 dt} dt + C\right]$$

$$G_2(t) = G_0 \frac{K_1}{K_2 - K_1}\left(e^{-K_1 t} - e^{-K_2 t}\right) + G_0 \qquad 3.9$$

For SITT data, the insulin is administered intravenously and therefore the response of plasma glucose will be very fast, making $K_2 >>> K_1$ at $t > 0$. Based on this, Equation (3.9) reduces to:

$$G_2(t) = G_0 e^{-Kt} + G_0 \qquad 3.10$$

The amount $G_2(t)$ (mg/dL) represent the blood glucose concentration, which is the output of the model given by Equation (3.9) as a function glucose concentration.

3.3.4 Sensitivity Analysis of Blood Glucose Concentration Model

The procedure followed in model identification and sensitivity analysis on blood glucose concentration model is shown in Figure 3.1. The SITT data was collected and rearranged into a single column such that it represents the output of the model. The dynamic model Equations (3.3) and (3.4) describing the SITT was identified and presented in Section 3.3. In order to implement the data on SensSB software, it is necessary to formulate the problem so that it can accommodate the experimental data. The model equation was solved with the MATLAB solver ode15s and local sensitivities are calculated with SENS_SYS. In the differential algebraic equations (DAEs) initialization stage, the necessary information to compute the function was provided, the SITT data has one state variable (plasma glucose concentration level) and the initial range for normoglycemic subject is 70-110 mg/dL

according to Diabetes Association of Nigeria (Chinenye, 2013). The data has 10 sampling points at [-10 0 2 4 6 8 10 12 14 16] measured in minutes. The system of ODEs involves 3 parameters, a name can be assign to them otherwise it would be generated automatically as 'p1', 'p2', 'p3'. Here p1, p2, and p3 represent K_1, K_2 and G_o respectively. The initial value chosen for the three parameters are [0.028 0.026 75], lower bound [0.01 0.01 60] and upper bound [0.03 0.03 80]. The 3 parameters to be estimated so the vector [1 2 3] must be introduced.

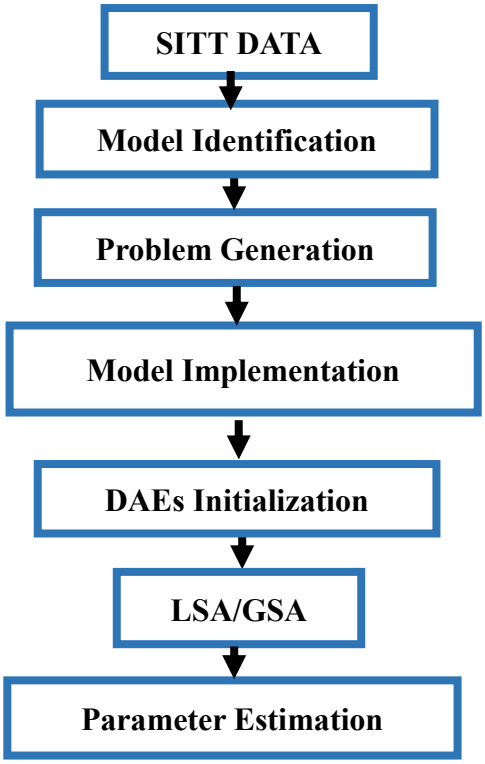


Figure 3.1: Procedure for model identification and sensitivity analysis.

3.3.5 Model Parameter Estimation

The blood glucose concentration of the subject explicitly based on the developed model needed to be regulated. This process requires fitting the parameters of the model to the specifications of the subjects, which are expected to vary considerably depending on the subject.

Since the level of glucose changes with respect to the type of meal taken, it is represented by a system of linear differential equation. One major challenge in system identification is to estimate the unknown parameters to verify regions of the system and the most relevant state variables (Rodriguez-Fernandez and Banga, 2010). Estimating the unknown parameters of a mathematical model requires the input-output data and the class of model (Jacobs, 2015). The parameters are chose so that the output of the model is the best match with respect to the experimental data (Jacobs, 2015).

The SITT data used as experimental data based on which the parameters of the model was estimated. Parameter estimation is implemented by the use of SensSB software Toolbox in MATLAB developed by Rodriguez-Fernandez and Banga (2010) relying on the maximum likelihood formulation, which allows good estimation in terms of fitting the physical model and parameter ranking. The model parameters are presented in Table 3.1.

Table 3.1: Model parameters

Parameter Symbol	**Units**	**Description**	**Values**	**Sources**
G_o	mg/dL	Plasma blood glucose concentration	$75\,mg/dL$	Gutti *et al.,* (2010)
K_1	$\min^{-1}$	Rate of food digestion	$0.028\,\min^{-1}$	Gutti *et al.,* (2010)
K_2	$\min^{-1}$	Rate of disappearance of glucose in blood compartment	$0.026\,\min^{-1}$	Gutti *et al.,* (2010)

3.3.6 Model Implementation in SensSB Software

The procedure for the model implementation is as follows:

- **Step 1**: A SensSB file named Abdul_Alim_Model is created in the Graphical User Interface (GUI) of the toolbox (Figure 3.2).



Figure 3.2: Problem Generation

- **Step 2**: The DAEs are written directly in option 3 of the GUI as shown in Figure 3.3

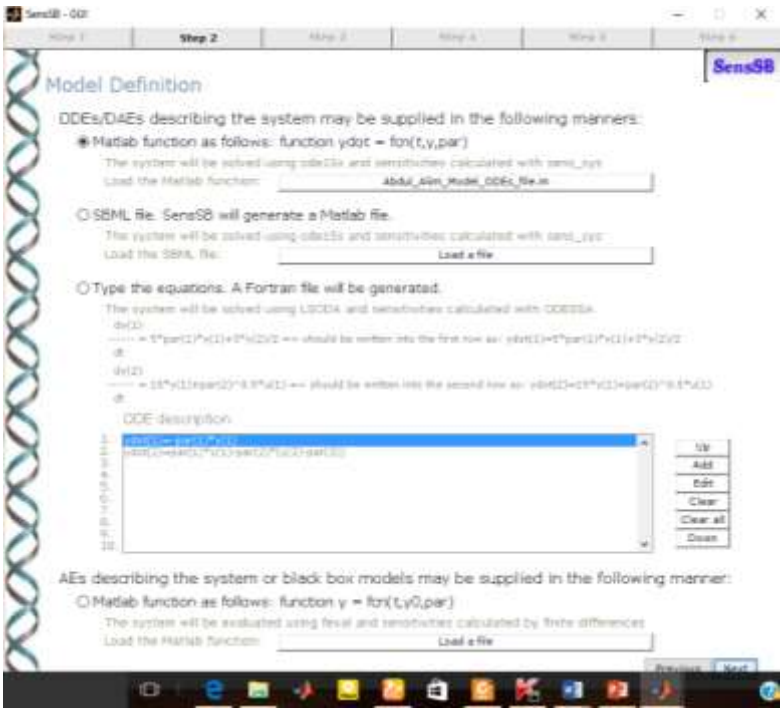


Figure 3.3: Model Implementation

- **Step 3**: ODEs initialization step

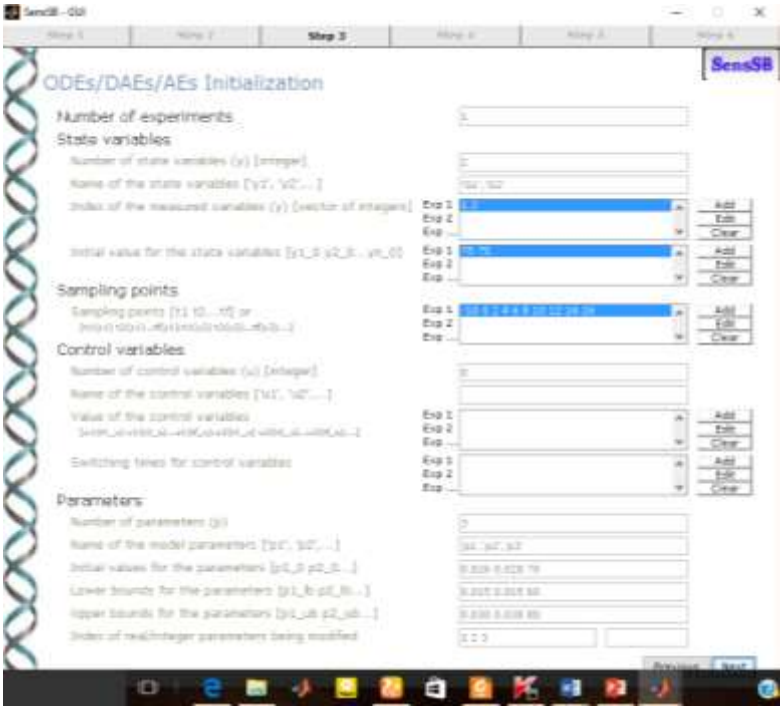


Figure 3.4: DAEs Initialization

- **Step 4**: Parameter estimation step

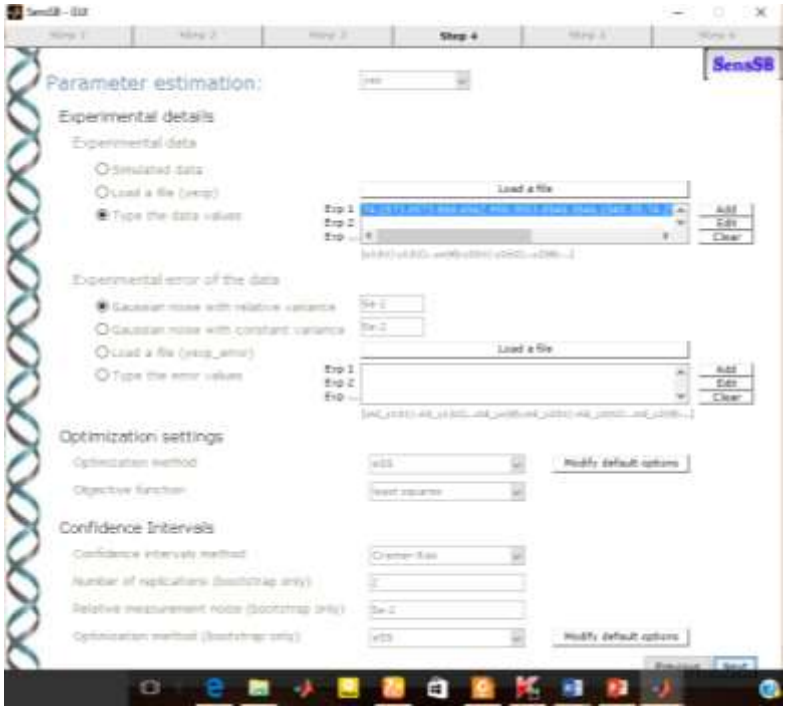


Figure 3.5: Parameter estimation settings

- **Step 5**: After the parameter estimation, a local identifiability analysis can help to identify correlations between parameters and low sensitivities.

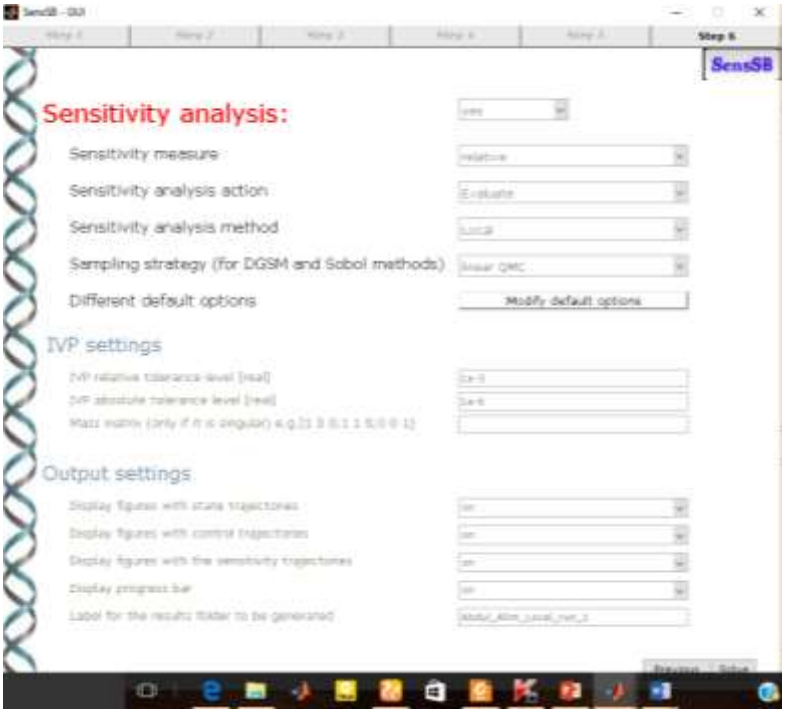


Figure 3.6: Local sensitivity analysis settings

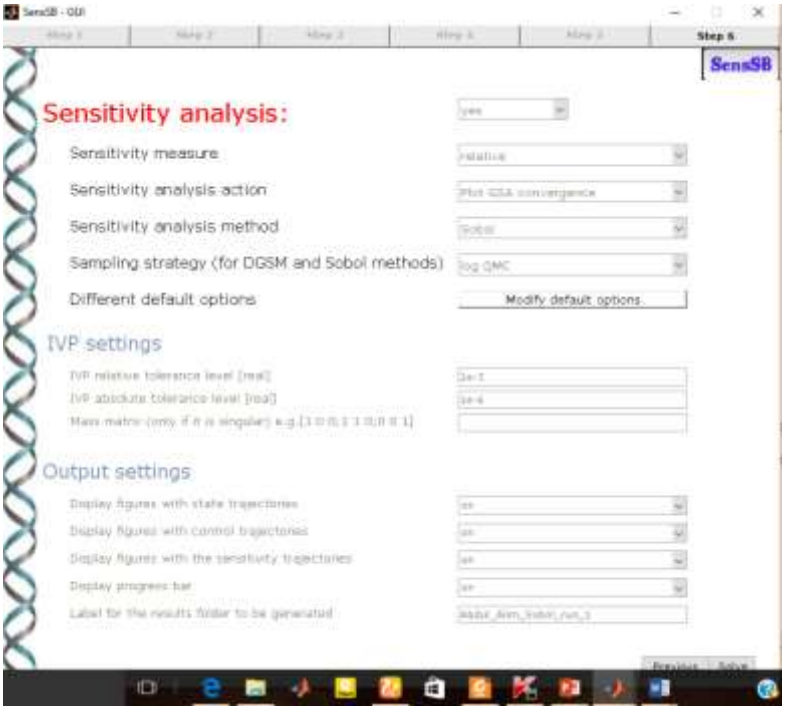


Figure 3.7: Global sensitivity analysis settings based on sobol' method

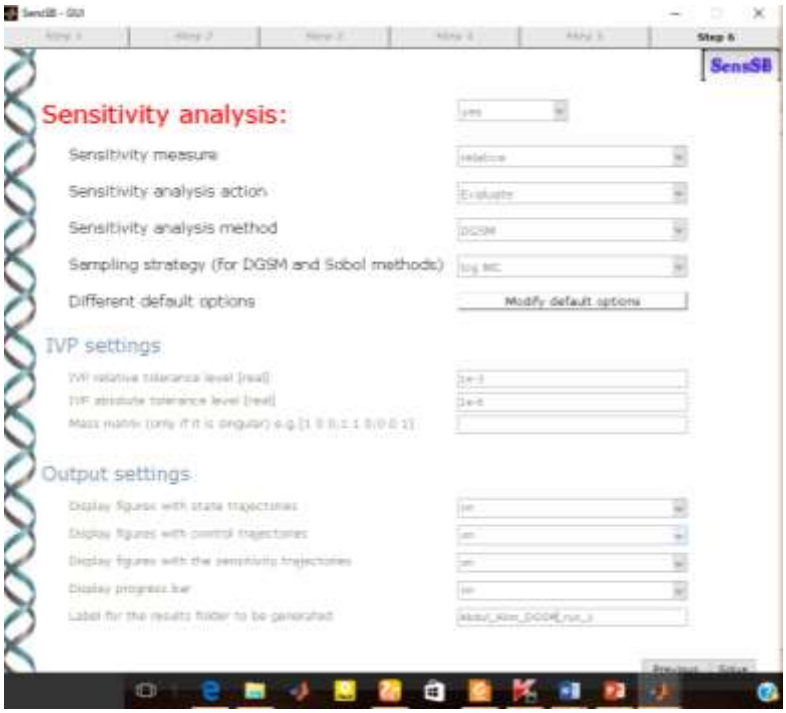


Figure 3.8: Global sensitivity analysis setting based on DGSM method

3.3.7 Control Structure

The main objective of this work, is to develop a control strategy under the model predictive control framework for regulating blood glucose concentration within the range of 70 – 120 mg/dL as recommended by Diabetes Association of Nigeria in Chinenye *et al* (2013). The objective function of the RHC to maintain blood glucose concentration around 100 mg/dL in this work is formulated as follows:

$$\min_{u(0),\ldots u(N)} J = \sum_{k=0}^{N_y} y'(k) Q y(k) + \sum_{k=0}^{N_u} u'(k) R u(k) \qquad 3.11$$

Subject to prediction model: for moving-end strategy

$$\dot{x}_{t+k+1|t} = A_t \dot{x}_{t+k|t} + B u_{t+k|t} + k e[t]$$

$$y_{t+k|t} = C \dot{x}_{t+k|t} + y(t) \qquad 3.12$$

Where $\dot{x}_{t+k|t}$, k= 0, 1,…, N_y, represents the predicted blood glucose concentration over finite horizon $[t, t+N_y]$, N_y is the prediction horizon defined in (1). $k \neq 0$, the matrices A, B, C, k are given in Appendix C. The manipulated variables constraints: $u_{k|t} = u_{N_u|t}$ for $k = N_u + 1, ..., N_y$ where N_u is the control horizon; $0 \leq u \leq u_{t+k|t} \leq \bar{u}$ for k = 0, 1,…, N_u.

Where u and $\bar{u}$ are lower and upper bounds of the control variable (blood glucose concentration) respectively. The bounds are set to avoid hypoglycemia.

The output constraints: $\dot{y}_{t+k|t} \geq y^*$ for k = 0, 1, …, N_y and y^* is set to be 80 mg/dL.

In the case of fixed end horizon strategy: $[t+1]$, the prediction model was subjected to:

$$\hat{x}_{t+1|t} = Ax(t) + Bu(t) + Ke(t)$$

$$y_{t+1|t} = Cx(t) + y(t) \qquad 3.13$$

Where $\hat{x}_{t+1|t}$, k = 0, 1,…, N_y, represents the predicted blood glucose concentration over finite horizon $[t+1]$, N_y is the prediction horizon defined in Equation (3.11).

The control algorithms proposed in this thesis to calculate the actual doses of insulin were based on a mathematical model of the patient dynamics. Moreover, they used predictions of the blood glucose concentration to take decisions about insulin intakes.

A linear state-space model was used in a prediction algorithm to predict future blood glucose concentration. The model structure, describing the patients' dynamics, was used within an optimization based control algorithm to determine the amounts of insulin to be applied to the patient.

3.3.8 Controller Design and Implementation

Based on the linear state space model, the controller was designed and afterwards implemented under the Model Predictive Control framework in MATLAB.

Generally, in the process of controller design, there are several parameters that determine the controller's performance and they were carefully specified.

The horizon specifications include the following:

1. *Control interval,* which specifies the length of time after which controller modifies the control action to track successfully the reference trajectory of the output.
2. *Prediction horizon,* which sets the number of control intervals in the course of which the output variables need to be optimized.
3. *Control horizon,* in contrast with prediction horizon, gives the number of manipulated variables needed to be optimized.

The tuning of the controller is made considering the following:

4. *Max down/up rates,* which define the maximum amount of corresponding decrease or increase in control variables in a single control interval.

Weights for inputs and outputs, which penalize deviations of manipulated variables from their nominal value and/or output from a reference set-point respectively.

Controller's settings are presented in Table 3.2; for the control interval, a 20-minute interval was chosen, taking into account that the system dynamics is quite slow, whereas for the prediction and control horizons the values selected were 30 and 25 minutes respectively. Regarding the weights, special attention was given in the output weight because it is essential for the controller to remain as close as possible to the optimal set point of 100 mg/dL glucose. By setting the maximum up rate equal to a small value, in this case 0.02, the controller's

action becomes less aggressive but at the same time the possibility of the patient's glucose to decrease significantly, reaching hypoglycemia, which is highly undesirable, is unlikely.

Table 3.2: Controller settings

Model	State space	Nominal
Horizon	**Control interval**	**20 min**
	Control horizon	**30 min**
	Prediction horizon	**25 min**
Manipulated variable	**Min**	**0.1 u/kg**
(Insulin)	**Max**	**0.5 u/kg**
	Max down rate	**0.08 u/kg**
	Max up rate	**0.02 u/kg**
	Weight	**1**
Control Variable	**Min**	**70 mg/dL**
(blood glucose	**Max**	**120 mg/dL**
concentration)	**Weight**	**5**

CHAPTER FOUR

RESULTS

INTRODUCTION

The results of the model developed, sensitivity analysis, and parameter estimation as well as the performance of the controller based on fixed and moving end strategies under different disturbance scenarios are presented in this chapter.

4.1 Dynamic Model

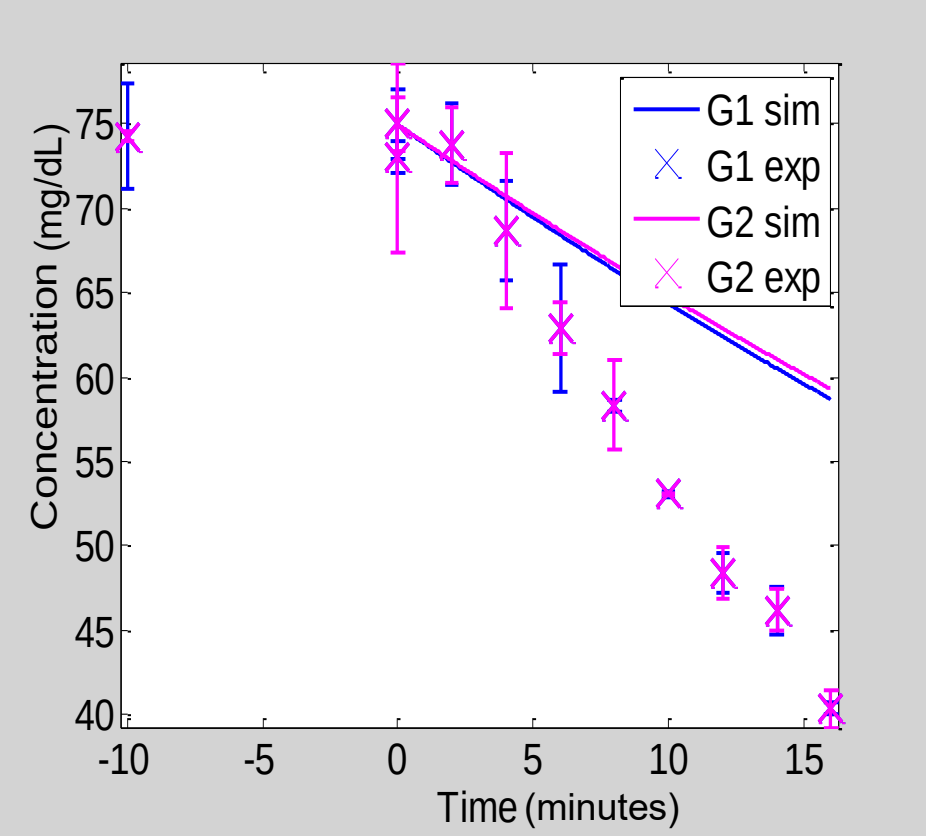


Figure 4.1: Fitted SITT data with dynamic model for control subject in SensSB

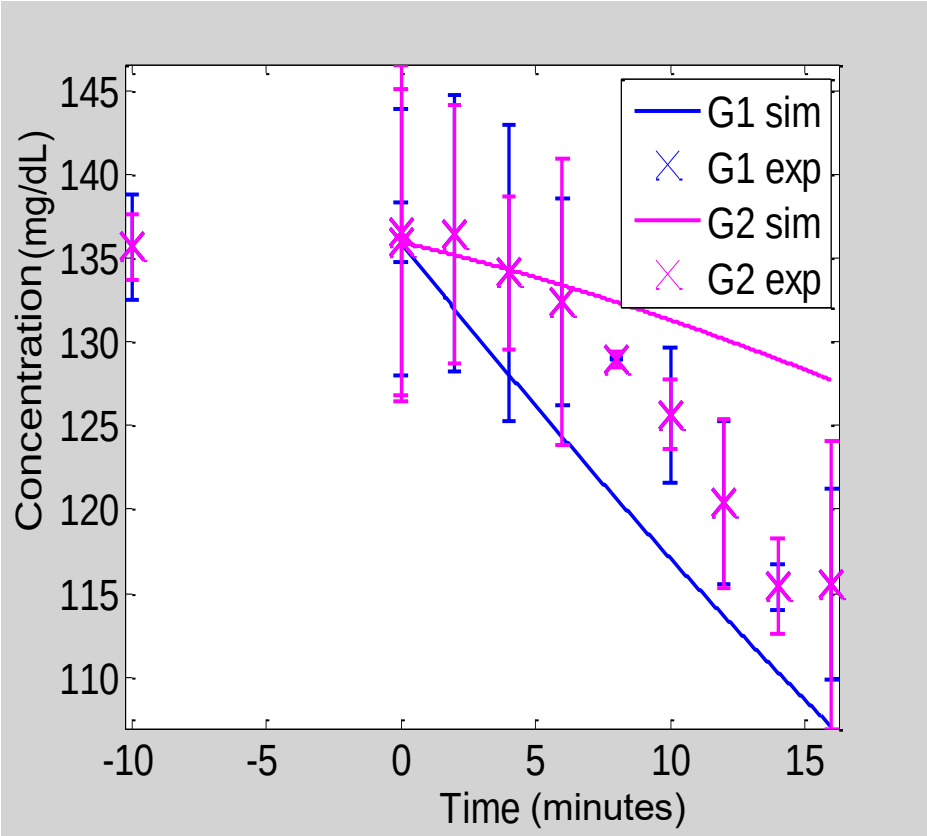


Figure 4.2: Fitted SITT data with dynamic model for diabetic subject in SensSB

4.2 Sensitivity Analysis of the Model

Here, the results for the sensitivity analysis of the model based on local, Sobol' and DGSM method in SensSB are presented.

Table 4.1: Local Sensitivity Analysis results

Ranking	Parameter	msqr	mabs	mean	min	max	abs_sens
1	P2	1.16e-001	4.02e-002	-4.02e-002	5.58e-012	-4.65e-001	8.10e+001
2	P1	8.78e-002	4.29e-002	-4.85e-003	2.08e-001	-2.88e-001	1.59e+002
3	P3	0.00e+000	0.00e+000	0.00e+000	0.00e+000	0.00e+000	0.00e+000

Where msqr is the parameter ranking based on the squared root of the square relative

sensitivities, mabs is the parameter ranking based on the mean of the absolute values of the relative sensitivities, mean represent the parameter ranking based on the mean of the relative sensitivities, min is the ranking based on the minimum value of the relative sensitivities, max is the ranking based on the maximum values of the relative sensitivities and abs_sens is the parameter ranking based on the mean of the absolute sensitivities.

Table 4.2: Global Sensitivity Analysis results based on Sobol' method

Parameter	SI_j	SI_j^T
P1	2.496e-001	8.293e-001
P2	7.504e-001	3.378e-001
P3	0.000e+000	0.000e+000

Table 4.3: Global Sensitivity Analysis results based on DGSM method

Parameter	abs_M_j^*	abs_sigma_j^*	rel_M_j^*	rel_sigma_j^*
P1	6.198e-001	6.160e-001	6.501e-001	6.219e-001
P2	3.802e-001	3.840e-001	3.499e-001	3.781e-001
P3	0.000e+000	0.000e+000	0.000e+000	0.000e+000

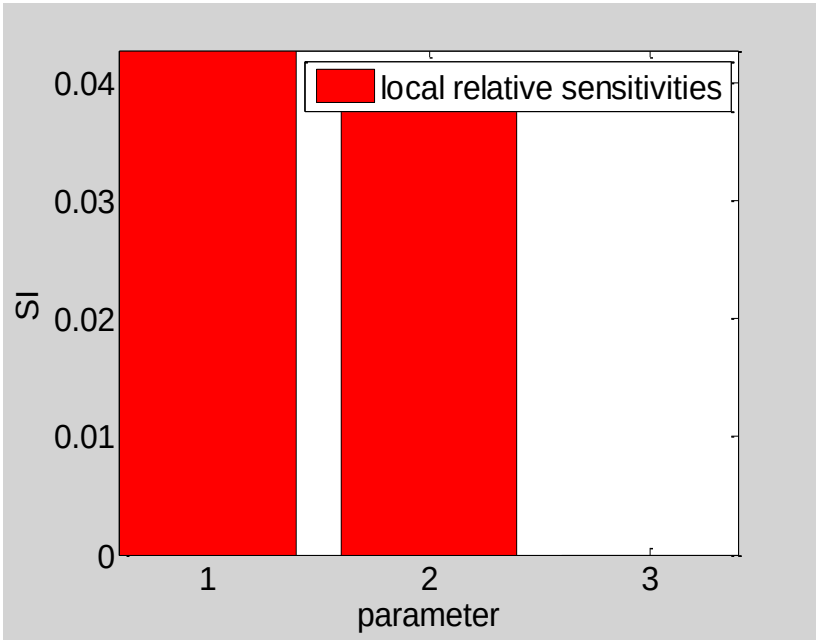


Figure 4.3: Parameter ranking based on local sensitivity method.

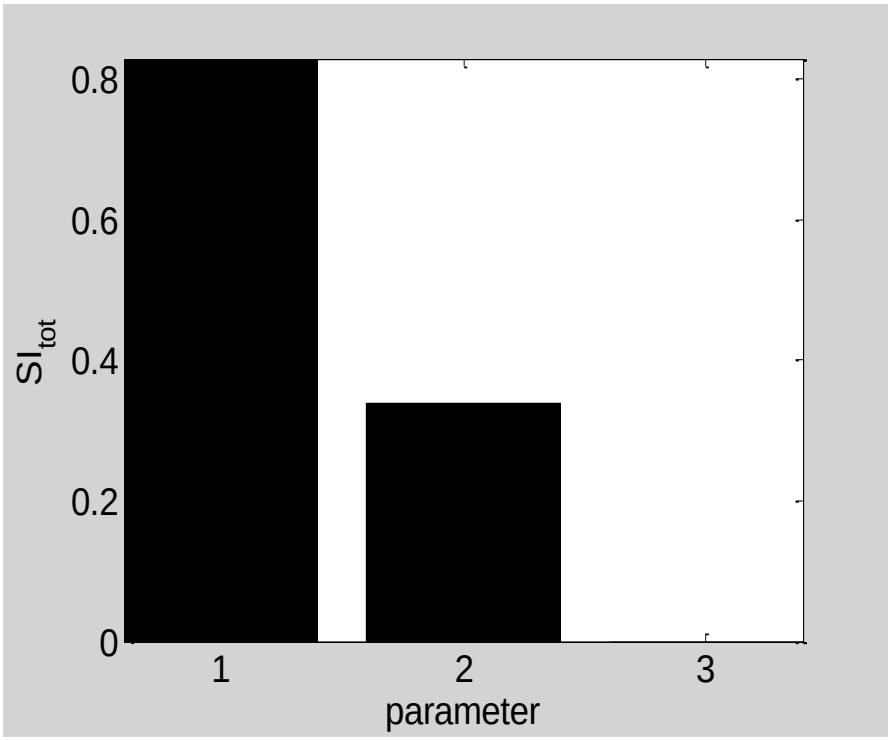


Figure 4.4: Parameter ranking based on Sobol' method of sensitivity analysis.

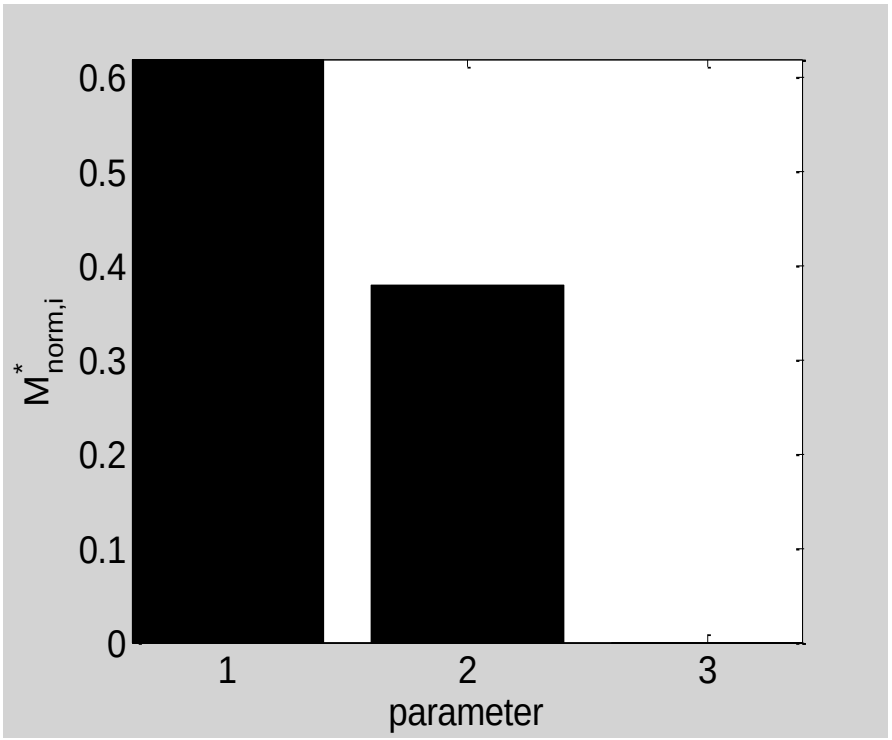


Figure 4.5: Parameter ranking based on DGSM method of sensitivity analysis.

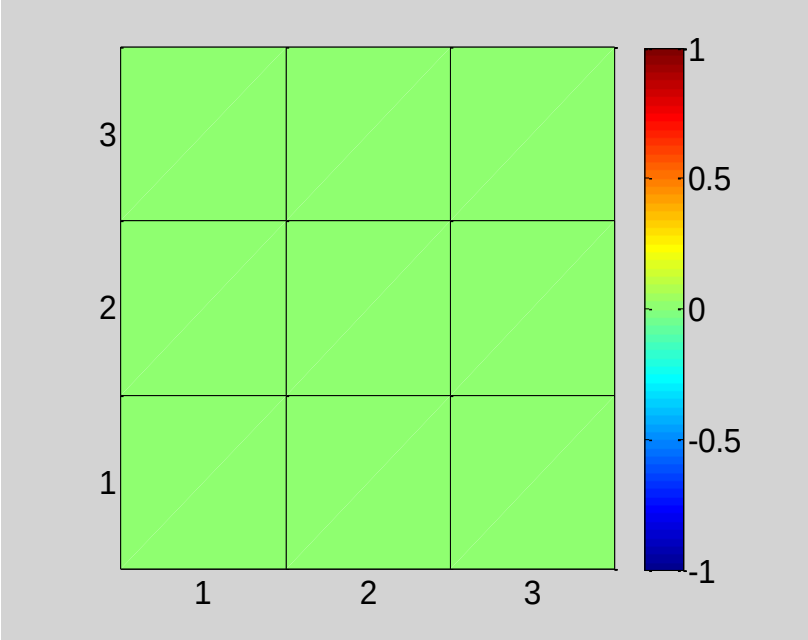


Figure 4.6: Correlation matrix based on GSA method

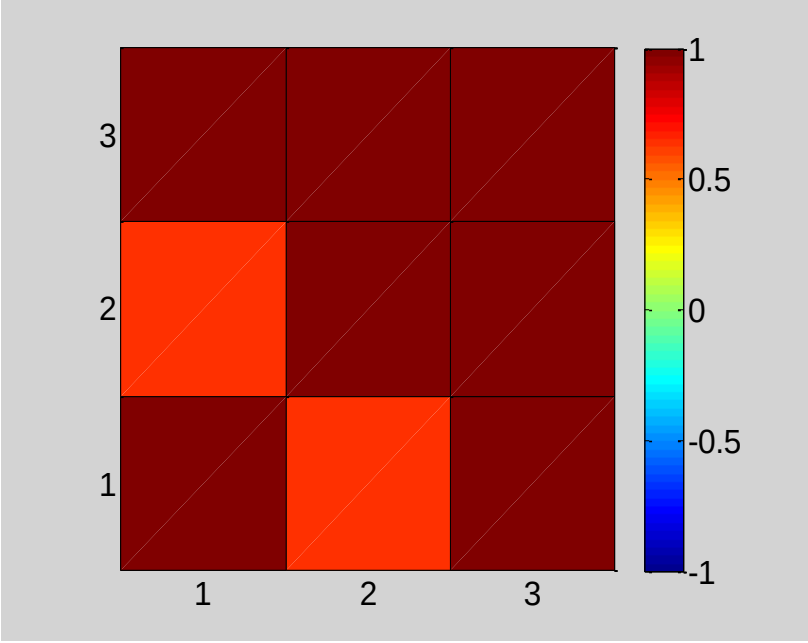


Figure 4.7: Correlation matrix based on local sensitivity method.

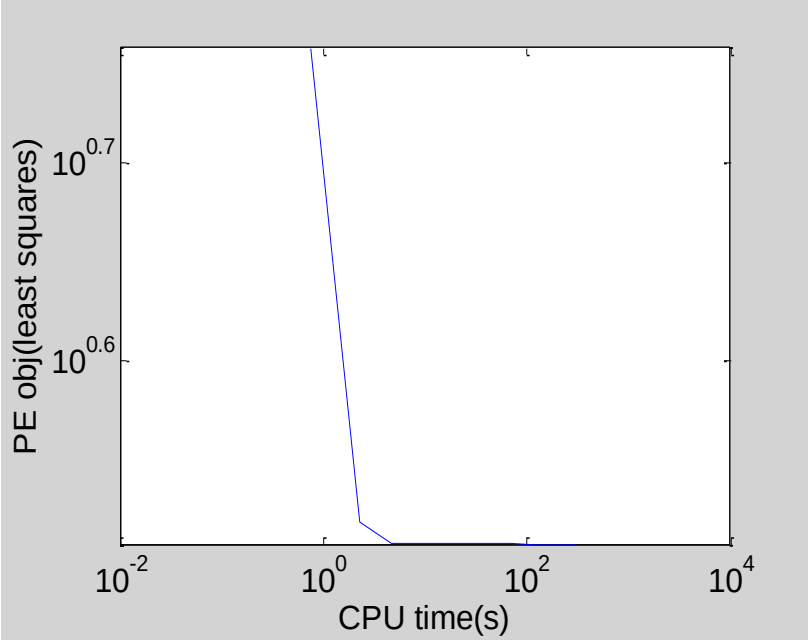


Figure 4.8: Convergence curve after parameter estimation based on local sensitivity method

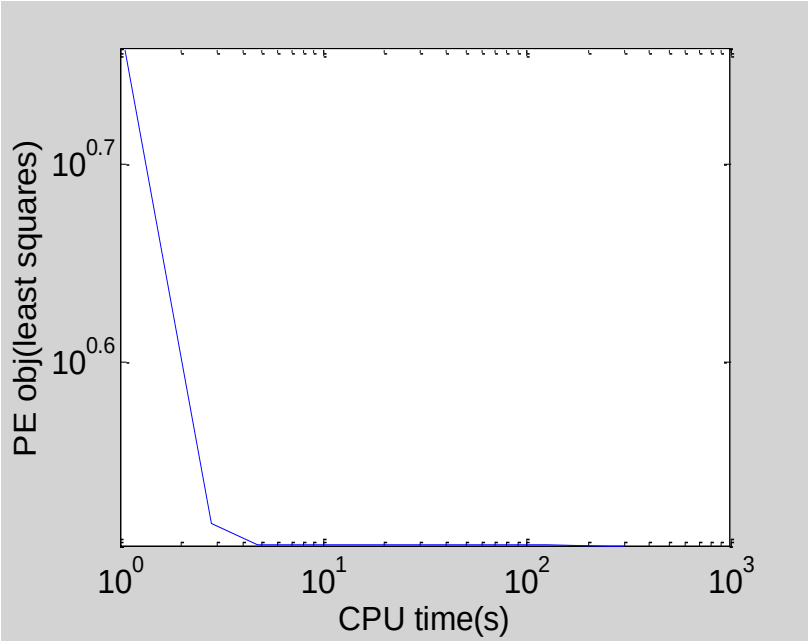


Figure 4.9: Convergence curve after parameter estimation based on GSA method.

4.3 Parameter Estimation of the Model

The results of the parameter estimation based on local, Sobol and DGSM method are presented in Tables 4.4, 4.5 and 4.6 respectively.

Table 4.4: Parameter estimation results based on local method

Optimal objective function value (least square) = 1.460e+000 **CPU time required for the estimation = 3.24e+002sec**		
Parameter	**Optimal value**	**Confidence interval (Cramer-Rao)**
P1	1.500e-002	+-2.689-004
P2	2.260e-002	+-3.537e-004
P3	7.590e+001	∞

Table 4.5: Parameter estimation results based on Sobol' method

Optimal objective function value (least square) = 1.216e+000 **CPU time required for the estimation = 3.00e+002sec**		
Parameter	**Optimal value**	**Confidence interval (Cramer-Rao)**
P1	1.607e-002	+-5.190e-004
P2	3.000e-002	+-7.232e-004
P3	6.970e+001	∞

Table 4.6: Parameter estimation results based on DGSM method

Optimal objective function value (least square) = 1.423e+000 **CPU time required for the estimation = 3.01e+002sec**		
Parameter	**Optimal value**	**Confidence interval (Cramer-Rao)**
P1	1.620e-002	+-4.931-004
P2	3.000e-002	+-6.859e-004
P3	6.171e+001	∞

4.4 Control Strategy

In order to demonstrate the performance of the fixed-end and moving-end horizon approaches, the state space model in Equations (3.12) and (3.13) with the set of constraints were deployed into the MATLAB workspace and modified to suit both of the control strategies. Set of simulation scenarios were performed and presented in this section in order

to serve as a comparative analysis between the fixed and moving-end horizon control strategies. The controller's action in five different disturbance scenarios are presented in Figures 4.10 to 4.14. In all the scenarios, the desired target is to minimize the variation in glucose level in the presence of input disturbances. However, the reference point was chosen to be 80 mg/dL, therefore, the glucose concentration (control variable) is expected to remain within 80 mg/dL when the external disturbance is suppressed.

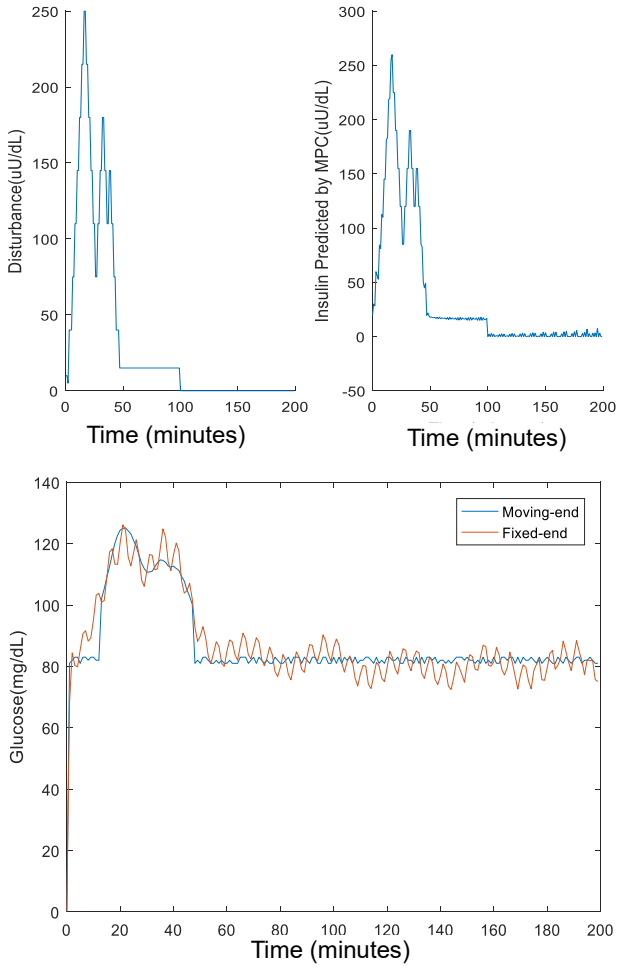


Figure 4.10: Performance of RHC controller with fixed-end (red) and moving-end (blue) for a diabetic subject fed with large quantity of (carbohydrate) disturbance.

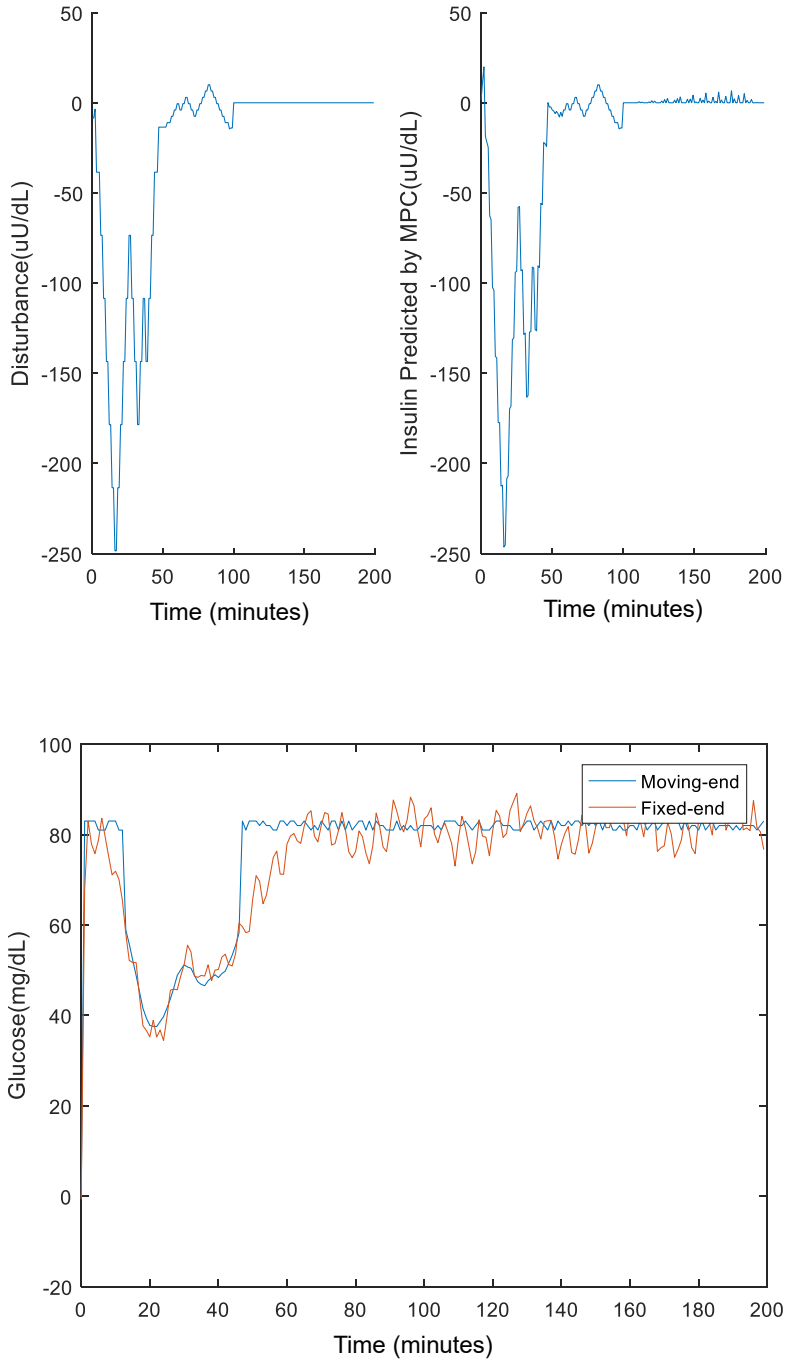


Figure 4.11: Performance of RHC controller with fixed-end (red) and moving-end (blue) for a diabetic subject fed with small quantity of (carbohydrate) disturbance.

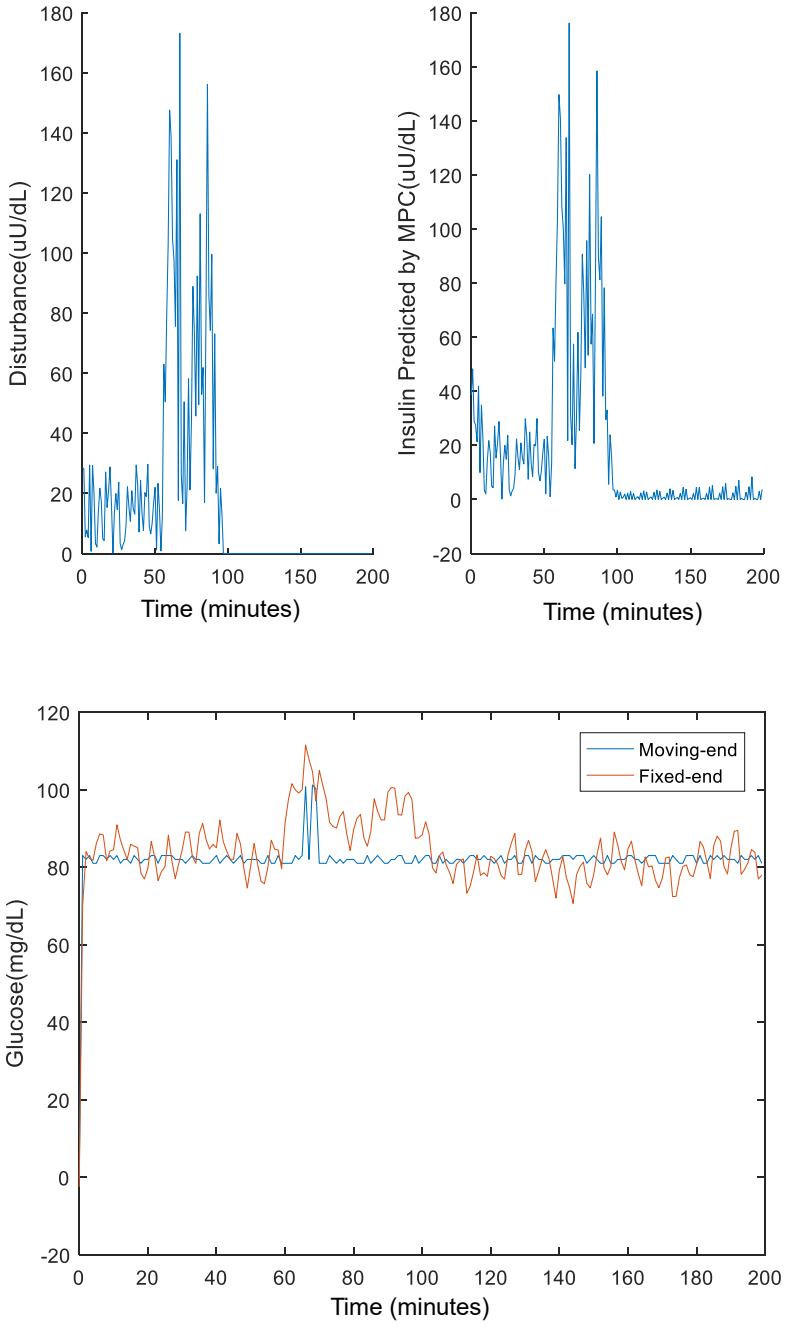
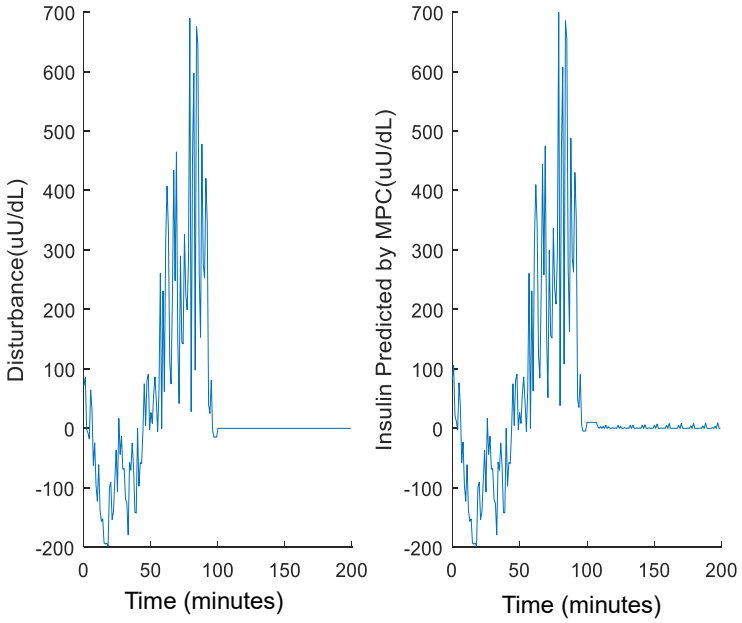


Figure 4.12: Performance of RHC controller with fixed-end (red) and moving-end (blue) for a control subject fed with large quantity of (carbohydrate) disturbance.



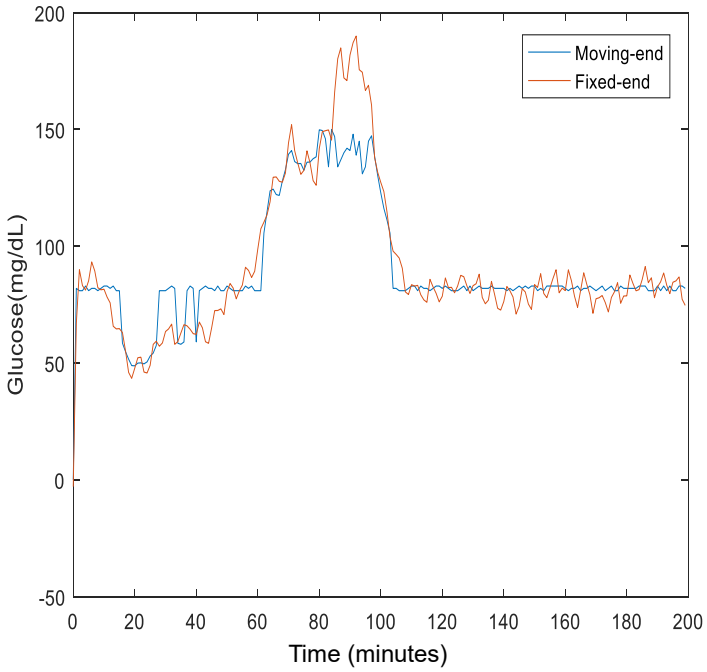


Figure 4.13: Performance of RHC controller with fixed-end (red) and moving-end (blue) for a male diabetic subject fed with large quantity of (carbohydrate) disturbance

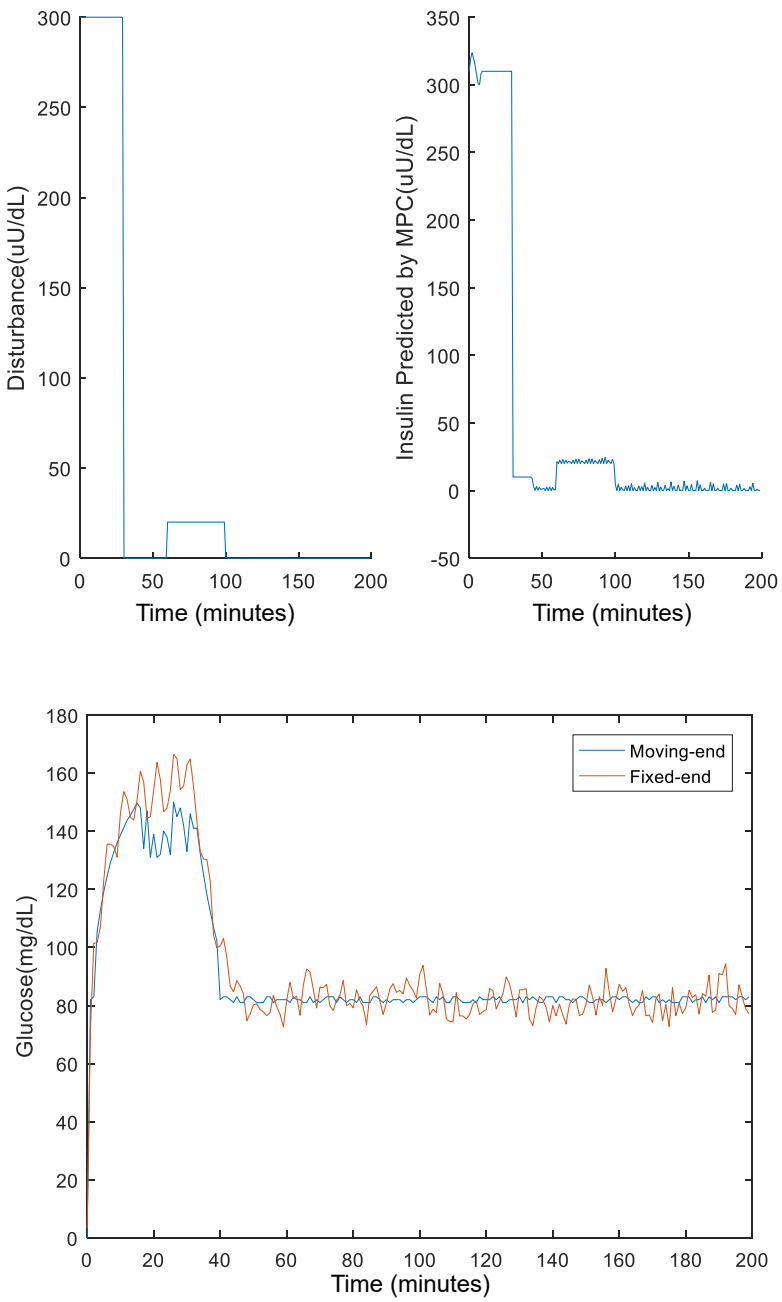


Figure 4.14: Performance of RHC controller with fixed-end (red) and moving-end (blue) for a male control subject fed with large quantity of (carbohydrate) disturbance.

CHAPTER FIVE
DISCUSSION

The results obtained for the dynamic model described in Equations (3.3) and (3.4) was fitted on SITT data and shows an appreciable consistence with the level of blood glucose concentration measured during SITT experiment. The dynamic model results obtained was compared with Estela, (2011) results which indicates a better fit on the SITT data. Figures 4.1 and 4.2 shows a comparison between the model predicted values and the SITT data reported by Gutti *et al.,* (2010), for a control and diabetic subject corresponding to the blood glucose concentration. It can be observed that the estimated parameters allow to reproduce almost exactly the experimental data while all the local solvers that was tried with this initial point failed to converge, or converged to bad local solutions. Different global solvers such as stochastic ranking evolutionary search (SRES) or differential equation (DE) also failed or converged in a much larger computational time. Subsequently, local and global sensitivity analysis were conducted to determine the most sensitive parameter of the model developed as shown in Tables 4.1, 4.2 and 4.3 for local, sobol and DGSM method respectively. It shows that the method can be easily implemented in MATLAB. The results of the sensitivity analysis further show that DGSM computation are reliable to a reasonable degree of accuracy. Sobol' method ranked the parameters in order of importance. Figures 4.3, 4.4 and 4.5 shows a parameter ranking based on local, Sobol' and DGSM method, it is a results of the sensitivity analysis which tells the parameters that are most important and the most likely parameters that affect the prediction of the model. The results of the DGSM computations are reliable to a certain degree of accuracy, Sobol' method still remain the ideal tool for ranking parameters in order of importance. The sensitivity analysis results show the model

is less sensitive to third parameter.

The correlation matrix is computed and convergence curve for the parameters are estimated, giving another measure of the goodness of the fit. The color plot of the correlation matrix in Figures 4.6 and 4.7 shows a good identifiability at the optimal value with maximum correlation coefficient of 0.75 between parameters 2 and 3. The results shows that the correlations are quite consistent along the parameter space. The computation of the global correlation matrix is time consuming compared to the local correlation matrix, so the time needed to reach convergence was higher than the one obtained with local method. Figures 4.8 and 4.9 shows a convergence curve after parameter estimation based on local and global method, the convergence error reach at 9.069e-003%, where a differential equation solver was used and converge in a much longer computational time due to the fact it tends towards more accurate and relatively better performance.

The results of the sensitivity analysis further indicate that for both local and global DGSM method, third parameter is less sensitive in the two cases. The parameter estimated based on DGSM differ from those obtained using local method due to the fact that DGSM depend on nominal values of the parameter. Estimated parameter values varies with different subjects and contradicts earlier reports by Sumner, (2010) who uses the principal components analysis to measure the importance of a parameter on the entire model output.

The parameter values estimated make use of the short insulin tolerance test data using local, Sobol' and DGSM results generated (Table 4.4, 4.5 and 4.6). The result obtained was used for the initial design vector of the model. A slight change in insulin sensitivity will have a larger impact in blood glucose control for the patient.

The LSA and GSA are assessed on the basis of the length of confidence intervals

computed for the parameter estimated with Cramer-Rao statistical method (Rodriguez-Fernandez & Banga, 2010).

To analyze the performance of fixed and moving-end horizon control, five scenarios of input disturbance are simulated. As discussed earlier, disturbance can be measured in terms of glucose concentration (mg/dL) in the blood stream resulting from direct injection of raw glucose over a specified time interval. However, all the simulation scenarios presented below serves to demonstrate the controller action in the presence of input disturbance and therefore do not represent any practical/real-time scenario. As such, all the input values were used in some cases to demonstrate the robustness of the developed controller.

Figures 4.10 to 4.14 represents the controller's action in five different disturbance scenarios describing the dynamics of eight groups of adult Nigerian subject. In all the scenarios, the desired target is to minimize the variation in glucose level in the presence of input disturbances. However, the reference point was chosen to be 80 mg/dL, therefore, the glucose concentration (control variable) is expected to remain within 80 mg/dL when the external disturbance is suppressed. It would be observed that the moving-end horizon control strategy presents a better stability/reference tracking than the fixed-end strategy. In Figure 4.10, the moving-end strategy can be seen to stabilize in about 50 minutes, whereas the counterpart approach did not settle (presented a poor tracking of the reference point 80 mg/dL) and the controller was able to calculate the actual amount of insulin of $(0.13\ \mu U/dL)$ required to regulate the blood glucose concentration. The results obtained were compared with Hamisu *et al.,* (2014) to evaluate the performance of the receding horizon control strategies. It was observed in Hamisu *et al.,* (2014) that the fixed end was suitable strategy

unlike the one obtained here, which demonstrate that moving end strategy is better alternative for blood glucose regulation. This happens as a result of differences in the set of data used in two of the such studies. In Figure 4.11, the moving-end strategy can be seen to also stabilize in about 50 minutes under different disturbance scenario, the fixed-end did not settle (presented a poor tracking of the reference point 80 mg/dL), and the controller was able to calculate the actual amount of insulin (0.13 $\mu U/dL$) required to regulate the blood glucose concentration. This could happen as a result of much exercise where blood glucose concentration goes below normal value. In Figure 4.12, the disturbance only resulted in a slight variation in the output of glucose concentration level (especially at the interval between 60 and 80 minutes). This means that the controller is robust enough to counter this effect, but in Hamisu *et al.,* (2014) the disturbance scenario affect the performance of RHC which makes the fixed end strategy a better alternative than the moving end. In Figure 4.13, due to the large quantity of disturbance, the moving-end based control strategy stabilizes (at about 92 mg/dL) immediately the disturbance was suppressed (100 minutes). Whereas, in Figure 4.14, the system settles in less than 40 minutes. The performance of the moving end strategy was compared with results obtained by Grema and Cao (2015), and it was observed that moving end provides a better alternative even with the effect of disturbance for blood glucose regulation.

Finally, the performance of receding horizon control based on fixed and moving end control strategies was conducted on different disturbance scenarios describing the dynamics of eight group of adult Nigerian subjects. The results show that, the moving end control strategy is a suitable alternative to control dynamic of blood glucose concentration. Moving end strategy represents better performance and stabilized with the given reference trajectory

under different disturbance scenarios. It keeps the blood glucose concentration steady at 80 mg/dL, which prevents the occurrence of hypoglycemia.

CHAPTER SIX
SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

5.1 SUMMARY

This thesis was summarized in chapters as follows;

In the first chapter, biomedical problem of glucose control using different control strategies in diabetes patients is analyzed. Type II diabetes mellitus is demonstrated as an example of biomedical system how the information content of clinical data from Short Insulin Tolerance Test (SITT) can be handled by optimal model-based estimation techniques is highlighted.

In the second chapter, modelling blood glucose-insulin system are presented, receding horizon control approach is introduced.

In the third chapter, global sensitivity analysis was performed to identify the most sensitive parameters of the patients to the glucose response. Parameters were estimated in a least square sense, useful results are achieved concerning the influence of key factors to the model output. Two forms of receding horizon approach (fixed and moving end strategies) was introduced in order to regulate blood glucose regulations.

In the fourth chapter, the results of sensitivity analysis and parameter estimation are presented. The performance of the controller in the presence of input disturbance was also analysed and discussed in chapter five.

In the sixth chapter, the most important findings of the research are concluded and recommendations for future studies are provided.

5.2 CONCLUSIONS

The problem facing biomedical system in regulating blood glucose concentration is exploited using short insulin tolerance test in type II diabetes as example. Specifically, a

sensitivity analysis was studied on the SITT data and two receding horizon control strategies were developed, which successfully regulate the blood glucose concentration.

Firstly, a dynamic model of blood glucose concentration was developed from SITT data obtained. The results of the developed model were very close to the SITT data, the error margin between the values simulated and SITT data reached at 9.069e-002%. This indicates that the dynamic model satisfactorily fit the data and can be used by the subjects to keep tract of their blood glucose level.

Secondly, a general sensitivity analysis was performed based on local and global DGSM method with the aim of identifying the most sensitive parameters, more specifically the ones related to dynamic model developed. The parameters were estimated in the least square sense, with SITT data fitting the dynamic model satisfactorily.

Finally, a receding horizon control based on fixed and moving end strategies was performed with the aim of regulating blood glucose concentration and calculating the actual amount of insulin dose required for blood glucose regulation. The results from sensitivity analysis were used to determine the optimal values of control and manipulated variable characterized by SITT data. Performance of the controller has been analyzed with respects to two control strategies (fixed and moving-end control strategies). The results shows the moving end control strategy is a suitable alternative to control dynamic of blood glucose concentration. Moving end strategy represents better performance and stabilized with the given reference trajectory under different disturbance scenarios. The controller was assessed for its ability to track the normoglycemic set point of 80.06 mg/dL for blood glucose level.

5.3 RECOMMENDATIONS

The future works should consider the following area of research as advancement to this work:

1. More data should be obtained to get a better impression of parameter variability between patients and more extreme meal intake and insulin injection schemes should be recorded, to get an indication of how well the model performs under abnormal circumstances.
2. The capability of the receding horizon controller can be enhanced using large data sets obtained from medical institution, through the development of a dynamic model using a model bank (several models developed for different individuals and store in a certain memory location). A suitable model can be selected to fit the behaviour of the patient's body system. This, however, can make the approach more realistic and useful in real-time diagnostic systems.
3. With the presence of AI techniques such as the ANN, large data sets can be used for training and the resulting model can be converted to the desired form and fed into MPC controller. This approach can be more accurate and additive to the changing body system.

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APPENDICES

APPENDIX A: The Short Insulin Tolerance Test (SITT) Data

Table A-1: Short Insulin Tolerance Test Data

Patients	Blood Glucose Concentration (mg/dL)									
	Time (min)									
	Fasting	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**
MC	70.542	70.12	65.958	64.708	63.708	58.63	56.875	50.708	48.042	43.375
FC	74.25	73.05	73.8	68.65	62.9	58.35	53.05	48.35	46.15	40.35
MD	144.15	145.35	145.96	141.38	139.31	134.9	132.81	127.27	122.81	118.08
FD	110	110.53	108.76	108.82	106.71	104.5	101.65	99	89.59	87.24
C≤35	70.69	70.97	68.24	64.83	62.14	56.69	53.52	48.59	45.79	40.31
C>35	75.2	72.4	72	69.73	65.67	61.8	58.27	51.67	49.87	45.27
D≤35	99.5	101	99	93.67	89.17	85	88.5	89.67	74.5	71.17
D>35	135.7	136.54	136.49	134.16	132.46	129	125.68	120.38	115.38	115.51

Note: MC = Male control, FC = Female control, MD = Male diabetic, FD = Female diabetic

C≤35 = Control subject ≤35 years, C>35 = Control subject >35 years

D≤35 = Diabetic subject ≤35 years, D>35 = Diabetic subject >35 years

B-8: Input file for dynamic model inplemented in SensSB based on local method

```
% This input file has been generated by SensSB_GUI
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%                         SensSB toolbox                   %
%                                                         %
% Copyright(C)(2010).                                        %
% Maria Rodriguez-Fernandez. mrodriguez@iim.csic.es              %
%                                                         %
% This toolbox is free of charge under the creative commons license.   %
% It is possible to find the conditions of the license on the         %
% following web page:                                        %
% www.creativecommons.org/licenses/by-nc-nd/3.0/                  %
%                                                         %
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

%----------------------------------------------------------------------%
%                         INPUT FILE                      %
% ------------------------------------------------------------------ %

function [input]          = Abdul_Alim_Model_input_file

%%
%----------------------------------------------------------------------%
%                     MODEL DEFINITION                     %
% ------------------------------------------------------------------ %
input.fcn_name            = 'Abdul_Alim_Model_ODEs_file';
input.fcn_type            = 'ODEs';
input.file_type           = 'Matlab';

%%
%----------------------------------------------------------------------%
%                 ODEs/DAEs INITIALIZATION                    %
% ------------------------------------------------------------------ %
input.n_exp              = [1]; % number of experiments
input.index_exp          = [1:1]; % index of the experiments in use

%Parameters
input.par_size           = 3; % number of parameters of the model
```

```
input.par_name           = char('p1','p2','p3'); % name of the model parameters
input.par_nominal        = [0.026 0.028 70]; % nominal value of the parameters
input.par_lb             = [0.015 0.015 60]; % lower bounds of the parameters
input.par_ub             = [0.030 0.030 80]; % upper bounds of the parameters
input.index_real_par     = [1 2 3]; % index of real parameters being modified
input.index_int_par      = []; % index of integer parameters being modified
input.index_par          = [1 2 3 ]; % index of parameters being modified

%State variables
input.n_states           = 2; % number of states of the model
input.states_name        = char('G1','G2'); % name of the state variables
input.index_states{1}    = [1  2]; % index of the measured states
input.y0{1}              = [75 75]; % initial value for the states
for iexp = input.index_exp
   input.yp0{iexp}       = zeros(input.n_states,input.par_size);
end

%Sampling points
for i_var=input.index_states{1}
   input.sampling_points{1}{i_var} = [-10   0   2   4   6   8  10  12  14  16]; % value of the
time sampling points
end

%Control variables
input.n_control_var      = 0; % number of control variables
input.control_var_name   = char(''); % name of the control variables
for iexp = input.index_exp
   input.control_times{iexp}   = []; % value of the switching times for the control
   input.control_var{iexp}     = []; % value of the control variables
end

%%
%-----------------------------------------------------------------------%
%                  PARAMETER ESTIMATION SETTINGS                        %
% ---------------------------------------------------------------- %

%Experimental details
input.exp_data{1}{1} = [74.25   73.05   73.8    68.65   62.9    58.35   53.05   48.35   46.15
40.35;]'; % experimental data
input.exp_data{1}{2} = [;74.25  73.05   73.8    68.65   62.9    58.35   53.05   48.35   46.15
40.35]'; % experimental data
for iexp = input.index_exp
   for i_var=input.index_states{iexp}
      input.data_error{iexp}{i_var} = []; % experimental data error
   end
end
```

```
for iexp = input.index_exp
   input.abs_error{iexp}  = []; % experimental data error
end
for iexp = input.index_exp
   input.rel_error{iexp}  = [5e-2]; % experimental data error
end

%Optimization settings
input.PE                = 'yes'; % parameter estimation action
input.PE_optimizer      = 'eSS'; % optimization method for the parameter estimation
input.PE_optimizer_options.eSS.maxtime      = 300; % Maximum CPU time in seconds
input.PE_optimizer_options.eSS.maxeval      = 1e7; % Maximum number of function
evaluations
input.PE_optimizer_options.eSS.local.solver   = 'dn2fb'; % Choose local solver
                                                % 0: Local search deactivated, 'fmincon'
                                                %
'fminsearchbnd','nomad','solnp','n2fb','dn2fb','dhc'
                                                % 'hj','ipopt','misqp','lsqnonlin'
input.PE_optimizer_options.eSS.log_var      = []; % Indexes of the variables which will
be used to generate
                                                %    diverse solutions in different orders of
magnitude
input.PE_obj            = 'least squares'; % objective function

%Confidence intervals
input.conf_int          = 'Cramer-Rao'; % confidence intervals method
input.ntrials           = 2; % number of replications for the bootstrap
input.bootstrap_noise   = 5e-2; % noise for the bootstrap replications
input.conf_optimizer    = 'eSS'; % optimization method for the bootstrap
input.conf_optimizer_options.eSS.maxtime      = 300; % Maximum CPU time in seconds
input.conf_optimizer_options.eSS.maxeval      = 1e7; % Maximum number of function
evaluations
input.conf_optimizer_options.eSS.local.solver   = 'dn2fb'; % Choose local solver
                                                % 0: Local search deactivated, 'fmincon'
                                                %
'fminsearchbnd','nomad','solnp','n2fb','dn2fb','dhc'
                                                % 'hj','ipopt','misqp','lsqnonlin'
input.conf_optimizer_options.eSS.log_var      = []; % Indexes of the variables which will
be used to generate
                                                %    diverse solutions in different orders of
magnitude

%%
%-------------------------------------------------------------------------%
%            OPTIMAL EXPERIMENTAL DESIGN SETTINGS                         %
% ----------------------------------------------------------------------- %
```

```
input.OED                   = 'no'; % OED action
input.index_control_var{1}    = []; % index of the control variables to be optimized
input.control_var_lb{1}       = []; % lower bounds for the control variables to be optimized
input.control_var_ub{1}       = []; % upper bounds for the control variables to be optimized
input.var_control_times       = 0; % 0 if fixed, 1 if variable;
input.steps_size_switching_lb = []; % lower bounds for the steps size
input.steps_size_switching_ub = []; % upper bounds for the steps size
input.index_control_y0{1}     = []; % index of the states which initial values are to be
optimized
input.control_y0_lb{1}        = []; % lower bounds for the states which initial values are to
be optimized
input.control_y0_ub{1}        = []; % upper bounds for the states which initial values are to
be optimized
input.index_time_var{1}       = []; % index of the states which sampling times are to be
optimized
input.steps_size_sampling_lb  = []; % lower bounds for the steps size
input.steps_size_sampling_ub  = []; % upper bounds for the steps size

%Optimization settings
input.OED_optimizer        = 'none'; % optimization method for the OED
input.OED_optimizer_options = []; % no options available
input.OED_method           = 'none'; % OED method
input.OED_parameter_scale      = 'linear'; % sampling scale
input.OED_parameter_distribution = 'MC_uniform'; % sampling distribution
input.OED_criterion        = 'Correlations average'; % objective function for the OED

%%
%------------------------------------------------------------------------%
%                  SENSITIVITY ANALYSIS SETTINGS                  %
% ---------------------------------------------------------------- %
input.SA                 = 'yes'; % sensitivity analysis yes/no
input.SA_measure           = 'relative'; % sensitivity analysis measure
input.SA_action          = 'evaluate'; % sensitivity analysis action
input.SA_method            = 'Local_SA'; % sensitivity analysis method
input.GSA_parameter_scale      = 'linear'; % sampling scale
input.GSA_parameter_distribution = 'QMC_uniform'; % sampling distribution

%%
% ------------------------------------------------- %
%                IVP SETTINGS                   %
% ------------------------------------------------- %
input.IVP_rel_tol          = 1e-3; % IVP relative tolerance
input.IVP_abs_tol          = 1e-6; % IVP absolute tolerance
input.M                  = []; % mass matrix

%%
```

```
% ------------------------------------------------- %
%                OUTPUT SETTINGS                    %
% ------------------------------------------------- %
input.states_plots       = 'on'; % Display figures with state trajectories
input.control_plots      = 'on'; % Display figures with control trajectories
input.sensitivity_plots  = 'on'; % Display figures with sensitivity trajectories
input.progress_bar   = 'on'; % Display progress bar
input.pname              = 'Abdul_Alim_Model'; % file name
input.label              = 'Abdul_Alim_Local_run_1'; % label for the results file
```

B-9: Input file for dynamic model inplemented in SensSB based Sobol' method

```
% This input file has been generated by SensSB_GUI
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%                        SensSB toolbox                        %
%                                                              %
% Copyright(C)(2010).                                          %
% Maria Rodriguez-Fernandez. mrodriguez@iim.csic.es            %
%                                                              %
% This toolbox is free of charge under the creative commons license.   %
% It is possible to find the conditions of the license on the          %
% following web page:                                          %
% www.creativecommons.org/licenses/by-nc-nd/3.0/               %
%                                                              %
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

%-----------------------------------------------------------------------%
%                        INPUT FILE                            %
% --------------------------------------------------------------------- %

function [input]         = Abdul_Alim_Model_input_file

%%
%-----------------------------------------------------------------------%
%                     MODEL DEFINITION                         %
% --------------------------------------------------------------------- %
input.fcn_name           = 'Abdul_Alim_Model_ODEs_file';
input.fcn_type           = 'ODEs';
input.file_type          = 'Matlab';

%%
```

```
%-------------------------------------------------------------------------%
%                  ODEs/DAEs INITIALIZATION                               %
% ----------------------------------------------------------------------- %
input.n_exp             = [1]; % number of experiments
input.index_exp         = [1:1]; % index of the experiments in use

%Parameters
input.par_size          = 3; % number of parameters of the model
input.par_name          = char('p1','p2','p3'); % name of the model parameters
input.par_nominal       = [0.026 0.028 70]; % nominal value of the parameters
input.par_lb            = [0.015 0.015 60]; % lower bounds of the parameters
input.par_ub            = [0.030 0.030 80]; % upper bounds of the parameters
input.index_real_par    = [1 2 3]; % index of real parameters being modified
input.index_int_par     = []; % index of integer parameters being modified
input.index_par         = [1 2 3 ]; % index of parameters being modified

%State variables
input.n_states          = 2; % number of states of the model
input.states_name       = char('G1','G2'); % name of the state variables
input.index_states{1}   = [1  2]; % index of the measured states
input.y0{1}             = [75 75]; % initial value for the states
for iexp = input.index_exp
   input.yp0{iexp}      = zeros(input.n_states,input.par_size);
end

%Sampling points
for i_var=input.index_states{1}
   input.sampling_points{1}{i_var} = [-10   0   2   4   6   8  10  12  14  16]; % value of the
time sampling points
end

%Control variables
input.n_control_var     = 0; % number of control variables
input.control_var_name  = char(''); % name of the control variables
for iexp = input.index_exp
   input.control_times{iexp}  = []; % value of the switching times for the control
   input.control_var{iexp}    = []; % value of the control variables
end

%%
%-------------------------------------------------------------------------%
%                  PARAMETER ESTIMATION SETTINGS                          %
% ----------------------------------------------------------------------- %

%Experimental details
```

```
input.exp_data{1}{1} = [74.25  73.05  73.8   68.65  62.9   58.35  53.05  48.35  46.15
40.35;]'; % experimental data
input.exp_data{1}{2} = [;74.25  73.05  73.8   68.65  62.9   58.35  53.05  48.35  46.15
40.35]'; % experimental data
for iexp = input.index_exp
   for i_var=input.index_states{iexp}
      input.data_error{iexp}{i_var} = []; % experimental data error
   end
end
for iexp = input.index_exp
   input.abs_error{iexp}  = []; % experimental data error
end
for iexp = input.index_exp
   input.rel_error{iexp}  = [5e-2]; % experimental data error
end

%Optimization settings
input.PE                = 'yes'; % parameter estimation action
input.PE_optimizer      = 'eSS'; % optimization method for the parameter estimation
input.PE_optimizer_options.eSS.maxtime      = 300; % Maximum CPU time in seconds
input.PE_optimizer_options.eSS.maxeval      = 1e7; % Maximum number of function
evaluations
input.PE_optimizer_options.eSS.local.solver   = 'dn2fb'; % Choose local solver
                                                % 0: Local search deactivated, 'fmincon'
                                                %
'fminsearchbnd','nomad','solnp','n2fb','dn2fb','dhc'
                                                % 'hj','ipopt','misqp','lsqnonlin'
input.PE_optimizer_options.eSS.log_var      = []; % Indexes of the variables which will
be used to generate
                                                %    diverse solutions in different orders of
magnitude
input.PE_obj            = 'least squares'; % objective function

%Confidence intervals
input.conf_int          = 'Cramer-Rao'; % confidence intervals method
input.ntrials           = 2; % number of replications for the bootstrap
input.bootstrap_noise   = 5e-2; % noise for the bootstrap replications
input.conf_optimizer    = 'eSS'; % optimization method for the bootstrap
input.conf_optimizer_options.eSS.maxtime      = 300; % Maximum CPU time in seconds
input.conf_optimizer_options.eSS.maxeval      = 1e7; % Maximum number of function
evaluations
input.conf_optimizer_options.eSS.local.solver   = 'dn2fb'; % Choose local solver
                                                % 0: Local search deactivated, 'fmincon'
                                                %
'fminsearchbnd','nomad','solnp','n2fb','dn2fb','dhc'
                                                % 'hj','ipopt','misqp','lsqnonlin'
```

```
input.conf_optimizer_options.eSS.log_var        = []; % Indexes of the variables which will
be used to generate
                                                %    diverse solutions in different orders of
magnitude

%%
%-------------------------------------------------------------------%
%            OPTIMAL EXPERIMENTAL DESIGN SETTINGS                   %
% ----------------------------------------------------------------- %
input.OED                   = 'no'; % OED action
input.index_control_var{1}    = []; % index of the control variables to be optimized
input.control_var_lb{1}       = []; % lower bounds for the control variables to be optimized
input.control_var_ub{1}       = []; % upper bounds for the control variables to be optimized
input.var_control_times       = 0; % 0 if fixed, 1 if variable;
input.steps_size_switching_lb = []; % lower bounds for the steps size
input.steps_size_switching_ub = []; % upper bounds for the steps size
input.index_control_y0{1}     = []; % index of the states which initial values are to be
optimized
input.control_y0_lb{1}        = []; % lower bounds for the states which initial values are to
be optimized
input.control_y0_ub{1}        = []; % upper bounds for the states which initial values are to
be optimized
input.index_time_var{1}       = []; % index of the states which sampling times are to be
optimized
input.steps_size_sampling_lb  = []; % lower bounds for the steps size
input.steps_size_sampling_ub  = []; % upper bounds for the steps size

%Optimization settings
input.OED_optimizer         = 'none'; % optimization method for the OED
input.OED_optimizer_options = []; % no options available
input.OED_method            = 'none'; % OED method
input.OED_parameter_scale      = 'linear'; % sampling scale
input.OED_parameter_distribution = 'MC_uniform'; % sampling distribution
input.OED_criterion         = 'Correlations average'; % objective function for the OED

%%
%-------------------------------------------------------------------%
%                  SENSITIVITY ANALYSIS SETTINGS                    %
% ----------------------------------------------------------------- %
input.SA                 = 'yes'; % sensitivity analysis yes/no
input.SA_measure           = 'relative'; % sensitivity analysis measure
input.SA_action            = 'evaluate'; % sensitivity analysis action
input.SA_method            = 'GSA_Sobol'; % sensitivity analysis method
input.GSA_parameter_scale      = 'logarithmic'; % sampling scale
input.GSA_parameter_distribution = 'QMC_uniform'; % sampling distribution
input.GSA_n                  = 10; % number of evaluations for GSA
```

```
%%
% ------------------------------------------------- %
%                  IVP SETTINGS                     %
% ------------------------------------------------- %
input.IVP_rel_tol         = 1e-3; % IVP relative tolerance
input.IVP_abs_tol         = 1e-6; % IVP absolute tolerance
input.M                   = []; % mass matrix

%%
% ------------------------------------------------- %
%                OUTPUT SETTINGS                    %
% ------------------------------------------------- %
input.states_plots        = 'on'; % Display figures with state trajectories
input.control_plots       = 'on'; % Display figures with control trajectories
input.sensitivity_plots   = 'on'; % Display figures with sensitivity trajectories
input.progress_bar   = 'on'; % Display progress bar
input.pname               = 'Abdul_Alim_Model'; % file name
input.label               = 'Abdul_Alim_Sobol_run_1'; % label for the results file
```

B-10: Input file for dynamic model inplemented in SensSB based on DGSM

```
% This input file has been generated by SensSB_GUI
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%                         SensSB toolbox                          %
%                                                                 %
% Copyright(C)(2010).                                             %
% Maria Rodriguez-Fernandez. mrodriguez@iim.csic.es               %
%                                                                 %
% This toolbox is free of charge under the creative commons license.   %
% It is possible to find the conditions of the license on the         %
% following web page:                                             %
% www.creativecommons.org/licenses/by-nc-nd/3.0/                  %
%                                                                 %
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

%-------------------------------------------------------------------%
%                         INPUT FILE                              %
% ----------------------------------------------------------------- %

function [input]          = Abdul_Alim_Model_input_file
```

```
%%
%-------------------------------------------------------------------%
%                      MODEL DEFINITION                             %
% ----------------------------------------------------------------- %
input.fcn_name          = 'Abdul_Alim_Model_ODEs_file';
input.fcn_type          = 'ODEs';
input.file_type         = 'Matlab';

%%
%-------------------------------------------------------------------%
%                  ODEs/DAEs INITIALIZATION                         %
% ----------------------------------------------------------------- %
input.n_exp             = [1]; % number of experiments
input.index_exp         = [1:1]; % index of the experiments in use

%Parameters
input.par_size          = 3; % number of parameters of the model
input.par_name          = char('p1','p2','p3'); % name of the model parameters
input.par_nominal       = [0.026 0.028 70]; % nominal value of the parameters
input.par_lb            = [0.015 0.015 60]; % lower bounds of the parameters
input.par_ub            = [0.030 0.030 80]; % upper bounds of the parameters
input.index_real_par    = [1 2 3]; % index of real parameters being modified
input.index_int_par     = []; % index of integer parameters being modified
input.index_par         = [1 2 3 ]; % index of parameters being modified

%State variables
input.n_states          = 2; % number of states of the model
input.states_name       = char('G1','G2'); % name of the state variables
input.index_states{1}   = [1  2]; % index of the measured states
input.y0{1}             = [75 75]; % initial value for the states
for iexp = input.index_exp
   input.yp0{iexp}      = zeros(input.n_states,input.par_size);
end

%Sampling points
for i_var=input.index_states{1}
   input.sampling_points{1}{i_var} = [-10   0   2   4   6   8  10  12  14  16]; % value of the
time sampling points
end

%Control variables
input.n_control_var     = 0; % number of control variables
input.control_var_name  = char(''); % name of the control variables
for iexp = input.index_exp
   input.control_times{iexp}  = []; % value of the switching times for the control
```

```
    input.control_var{iexp}       = []; % value of the control variables
end

%%
%-------------------------------------------------------------------------%
%                   PARAMETER ESTIMATION SETTINGS                         %
% ----------------------------------------------------------------------- %

%Experimental details
input.exp_data{1}{1} = [74.25   73.05   73.8    68.65   62.9    58.35   53.05   48.35   46.15
40.35;]'; % experimental data
input.exp_data{1}{2} = [;74.25  73.05   73.8    68.65   62.9    58.35   53.05   48.35   46.15
40.35]'; % experimental data
for iexp = input.index_exp
    for i_var=input.index_states{iexp}
        input.data_error{iexp}{i_var} = []; % experimental data error
    end
end
for iexp = input.index_exp
    input.abs_error{iexp}  = []; % experimental data error
end
for iexp = input.index_exp
    input.rel_error{iexp}  = [5e-2]; % experimental data error
end

%Optimization settings
input.PE                = 'yes'; % parameter estimation action
input.PE_optimizer      = 'eSS'; % optimization method for the parameter estimation
input.PE_optimizer_options.eSS.maxtime       = 300; % Maximum CPU time in seconds
input.PE_optimizer_options.eSS.maxeval       = 1e7; % Maximum number of function
evaluations
input.PE_optimizer_options.eSS.local.solver   = 'dn2fb'; % Choose local solver
                                                % 0: Local search deactivated, 'fmincon'
                                                %
'fminsearchbnd','nomad','solnp','n2fb','dn2fb','dhc'
                                                % 'hj','ipopt','misqp','lsqnonlin'
input.PE_optimizer_options.eSS.log_var       = []; % Indexes of the variables which will
be used to generate
                                                %    diverse solutions in different orders of
magnitude
input.PE_obj            = 'least squares'; % objective function

%Confidence intervals
input.conf_int          = 'Cramer-Rao'; % confidence intervals method
input.ntrials           = 2; % number of replications for the bootstrap
input.bootstrap_noise     = 5e-2; % noise for the bootstrap replications
```

```
input.conf_optimizer      = 'eSS'; % optimization method for the bootstrap
input.conf_optimizer_options.eSS.maxtime        = 300; % Maximum CPU time in seconds
input.conf_optimizer_options.eSS.maxeval        = 1e7; % Maximum number of function
evaluations
input.conf_optimizer_options.eSS.local.solver    = 'dn2fb'; % Choose local solver
                                                  % 0: Local search deactivated, 'fmincon'
                                                  %
'fminsearchbnd','nomad','solnp','n2fb','dn2fb','dhc'
                                                  % 'hj','ipopt','misqp','lsqnonlin'
input.conf_optimizer_options.eSS.log_var        = []; % Indexes of the variables which will
be used to generate
                                                  %    diverse solutions in different orders of
magnitude

%%
%-------------------------------------------------------------------------%
%             OPTIMAL EXPERIMENTAL DESIGN SETTINGS                        %
% ----------------------------------------------------------------------- %
input.OED                  = 'no'; % OED action
input.index_control_var{1}    = []; % index of the control variables to be optimized
input.control_var_lb{1}       = []; % lower bounds for the control variables to be optimized
input.control_var_ub{1}       = []; % upper bounds for the control variables to be optimized
input.var_control_times       = 0; % 0 if fixed, 1 if variable;
input.steps_size_switching_lb = []; % lower bounds for the steps size
input.steps_size_switching_ub = []; % upper bounds for the steps size
input.index_control_y0{1}     = []; % index of the states which initial values are to be
optimized
input.control_y0_lb{1}        = []; % lower bounds for the states which initial values are to
be optimized
input.control_y0_ub{1}        = []; % upper bounds for the states which initial values are to
be optimized
input.index_time_var{1}       = []; % index of the states which sampling times are to be
optimized
input.steps_size_sampling_lb  = []; % lower bounds for the steps size
input.steps_size_sampling_ub  = []; % upper bounds for the steps size

%Optimization settings
input.OED_optimizer        = 'none'; % optimization method for the OED
input.OED_optimizer_options = []; % no options available
input.OED_method           = 'none'; % OED method
input.OED_parameter_scale      = 'linear'; % sampling scale
input.OED_parameter_distribution = 'MC_uniform'; % sampling distribution
input.OED_criterion        = 'Correlations average'; % objective function for the OED

%%
%-------------------------------------------------------------------------%
```

```
%                 SENSITIVITY ANALYSIS SETTINGS                 %
% ------------------------------------------------------------- %
input.SA                = 'yes'; % sensitivity analysis yes/no
input.SA_measure        = 'relative'; % sensitivity analysis measure
input.SA_action         = 'evaluate'; % sensitivity analysis action
input.SA_method         = 'GSA_DGSM'; % sensitivity analysis method
input.GSA_parameter_scale      = 'logarithmic'; % sampling scale
input.GSA_parameter_distribution = 'MC_uniform'; % sampling distribution
input.GSA_n             = 10; % number of evaluations for GSA

%%
% ------------------------------------------------- %
%                 IVP SETTINGS                      %
% ------------------------------------------------- %
input.IVP_rel_tol       = 1e-3; % IVP relative tolerance
input.IVP_abs_tol       = 1e-6; % IVP absolute tolerance
input.M                 = []; % mass matrix

%%
% ------------------------------------------------- %
%               OUTPUT SETTINGS                     %
% ------------------------------------------------- %
input.states_plots      = 'on'; % Display figures with state trajectories
input.control_plots     = 'on'; % Display figures with control trajectories
input.sensitivity_plots = 'on'; % Display figures with sensitivity trajectories
input.progress_bar      = 'on'; % Display progress bar
input.pname             = 'Abdul_Alim_Model'; % file name
input.label             = 'Abdul_Alim_DGSM_run_1'; % label for the results file
```

B-11: ODEs file inplemented in SensSB

```
% This input file has been generated by SensSB_GUI
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%                       SensSB toolbox                          %
%                                                               %
% Copyright(C)(2010).                                           %
% Maria Rodriguez-Fernandez. mrodriguez@iim.csic.es             %
%                                                               %
% This toolbox is free of charge under the creative commons license.   %
% It is possible to find the conditions of the license on the         %
% following web page:                                           %
% www.creativecommons.org/licenses/by-nc-nd/3.0/                %
%                                                               %
```

```
%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

%-----------------------------------------------------------------%
%                    ODEs FILE                    %
% --------------------------------------------------------------- %

function ydot=Abdul_Alim_Model_ODEs_file(t,y,par)
global control_var
ydot(1)=-par(1)*y(1);
ydot(2)=par(1)*y(1)-par(2)*(y(2)-par(2));
ydot=ydot';
```

B-12: FIXED-END AND MOVING-END RECEDING HORIZON STRATEGIES

```
function close_loop(PGL_C,mpc1_RefSignal, mpc1_MDSignal,n)
%% create MPC controller object with sample time
mpc1 = mpc(PGL_C, 1);
mpc1_LDSignal=mpc1_Signal(n);
[Y,T,U]=MPC(mpc1_LDSignal,mpc1_RefSignal, mpc1_MDSignal,mpc1);
Y0=Y;
for i=1:length(Y0)
   if abs(Y0(i)-80)<20
      Y0(i)=80+randi(3);
   end
      if Y0(i)-80>70
         Y0(i)=130+randi(20);
      end
end
subplot(1,2,1)
hold on
plot(T,mpc1_LDSignal(:,1))
ylabel('Disturbance(uU/dL)')
xlabel('Time(minutes)')
subplot(1,2,2)
hold on
plot(T,U(:,1))
xlabel('Time(minutes)')
ylabel('Insulin Predicted by MPC(uU/dL)')
figure
plot(T,Y0,T,Y+Y.*sin(2*pi*T/30)/25+Y.*sin(2*pi*T/5)/20+randi(8)*(0.5-rand(size(Y))))
xlabel('Time(minutes)')
ylabel('Glucose(mg/dL)')
legend('Moving-end','Fixed-end')
```

```
function mpc1_LSignal=mpc1_Signal(n)

mpc1_LSignal=...
[
   10     0     0
   10     0     0
    5     0     0
   40     0     0
   40     0     0
   40     0     0
   75     0     0
   75     0     0
  110     0     0
  110     0     0
  145     0     0
  145     0     0
  180     0     0
  180     0     0
  215     0     0
  215     0     0
  250     0     0
  250     0     0
  215     0     0
  215     0     0
  180     0     0
  180     0     0
  145     0     0
  145     0     0
  110     0     0
  110     0     0
   75     0     0
   75     0     0
  110     0     0
  110     0     0
  145     0     0
  145     0     0
  180     0     0
  180     0     0
  145     0     0
  145     0     0
  110     0     0
  110     0     0
  145     0     0
  145     0     0
  110     0     0
  110     0     0
```

```
   75    0    0
   75    0    0
   40    0    0
   40    0    0
   40    0    0
   15    0    0
   15    0    0
   15    0    0];
if n==0
mpc1_LSignal=[mpc1_LSignal;0*mpc1_LSignal];
end
if n==1
mpc1_LSignal=[flipud(mpc1_LSignal)/10;0*mpc1_LSignal]-
[mpc1_LSignal;0*mpc1_LSignal];
end
if n==2
mpc1_LSignal=[30*round(flipud(mpc1_LSignal)/30).*rand(size(mpc1_LSignal));0*mpc1
_LSignal];
end
if n==3
mpc1_LSignal=[30*round(flipud(mpc1_LSignal)/30).*rand(size(mpc1_LSignal));0*mpc1
_LSignal]/0.25+0.5*[flipud(mpc1_LSignal)/10;0*mpc1_LSignal]-
[mpc1_LSignal;0*mpc1_LSignal];
end
if n==4
  mpc1_LSignal=[[300*ones(30,1);zeros(30,1);20*ones(40,1);zeros(100,1)],zeros(200,2)];
end
```

APPENDIX C: The state space model matrix

C-1: Matrix of the state space model

$$A=\begin{bmatrix} 0.8145 & -0.6768 & -0.007007 & 0.2212 & -0.1378 & 0.2756 & 0.1406 & -0.2134 \\ 1.173 & -0.07853 & 19.95 & 8.244 & -12.9 & 21.6 & 3.462 & -9.414 \\ 0.1671 & -10.19 & -5.211 & -28.76 & 12.97 & -36.74 & -3.436 & 12.49 \\ 0.0424 & 0.1859 & 17.23 & 1.364 & 12.26 & -51.04 & 1.446 & 5.967 \\ 0.1548 & 0.6689 & 1.33 & -4.288 & -3.122 & 58.06 & 0.592 & -8.538 \\ -0.3731 & -0.329 & -0.5628 & 1.51 & -3.108 & -8.311 & 2.562 & 61.5 \\ -0.2807 & -0.3408 & 0.1154 & 0.8775 & 0.671 & -19.63 & -6.866 & -91.57 \\ 0.01318 & 0.2577 & -0.434 & -0.7708 & 0.8672 & -31.47 & 87.91 & -2.587 \end{bmatrix}$$

$$B=\begin{bmatrix} -1.441e-06 \\ -0.001224 \\ 0.001832 \\ 0.001948 \\ -0.002119 \\ -0.002934 \\ 0.005491 \\ 0.006215 \end{bmatrix}$$

$$C=\begin{bmatrix} 4674 & -28.02 & -7.984 & 2.53 & 2.14 & -0.05628 & 0.003985 & 0.07942 \end{bmatrix}$$

$$K=\begin{bmatrix} 0.1241 \\ -0.6815 \\ -0.5361 \\ 0.04596 \\ 0.04931 \\ -0.08173 \\ -0.1935 \\ 0.03915 \end{bmatrix}$$