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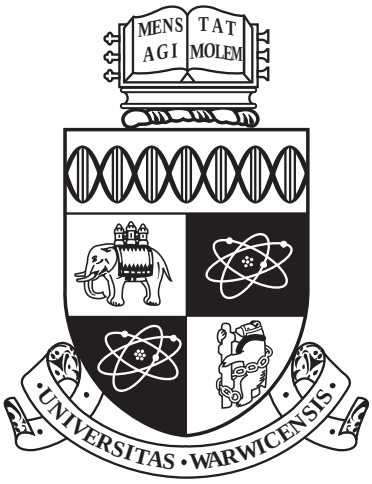

Structural Identifiability and Indistinguishability Analyses of Glucose-Insulin Models

by

Sze Vone Chin

Thesis

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Declarations

The thesis contains the original work by the author, with the following publications.

S.V. Chin and M.J. Chappell. Structural Identifiability and Indistinguishability analyses of the Minimal Model and a Euglycemic Hyperinsulinemic Clamp Model for Glucose-Insulin Dynamics, *Computater Methods Programs in Biomedicine*, 15 pages, In Press, 2011.

S.V. Chin and M.J. Chappell. Structural Identifiability of the Minimal Model and a Euglycemic Hyperinsulinemic Clamp Model for Glucose-Insulin Dynamics, *Proceedings of the 7th International Federation of Automatic Control (IFAC) Symposium on Modelling and Control in Biomedical Systems*, Aalborg, Denmark, 97-102, 2009.

In preparation for publication:
S.V. Chin and M.J. Chappell and P. Arundel. Structural Identifiability and reparameterisation of the Closed-Loop Minimal Model.

Abstract

In this thesis, the structural identifiability analyses of established and novel glucose-insulin models was performed, to determine whether the models are globally structurally identifiable with the observations available. Structural identifiability analysis is an essential step in the modelling process and a key prerequisite to experimental design and parameter estimation. Analyses were performed assuming observations of both glucose and insulin concentrations on two versions of the well-cited Minimal Model (MM), the Original Minimal Model (OMM) and Extended Minimal Model (EMM) for the modelling of the responses to an Intravenous Glucose Tolerance Test (IVGTT); a Euglycemic Hyperinsulinemic Clamp model and two novel modified versions of the MM, a Closed-Loop Minimal Model (CLMM) and a Double-Pole in Closed-Loop Minimal Model (DPCLMM), when the models describe a complete course of glucose-insulin dynamics during an IVGTT. The CLMM proved to be unidentifiable so a reparameterisation procedure was performed on this model, yielding a globally structurally identifiable reparameterised model. Parameter estimation using these models was also performed for sets of IVGTT and glucose clamp data. The results of the parameter estimation demonstrated that global structural identifiability does not as always guarantee numerical identifiability, or vice versa. A structural indistinguishability analysis was also performed to compare the MM and the CLMM, given the same observations, where it was shown that both models are distinguishable over both pre- and post- insulin switching phases. This is the first time that all such analyses have been performed on these specific model structures. The generic and numerical results obtained demonstrate issues that may arise in practice when attempting to calculate insulin sensitivity when using such models.

Abbreviations

CLMM	Closed-Loop Minimal Model
CRC	Controllability Rank Criterion
DPCLMM	Double-Pole Closed-Loop Minimal Model
EMM	Extended version of Minimal Model
EIC	Euglycemic Hyperinsulinemic Clamp
IDF	International Diabetes Federation
IDDM	Insulin Dependent Diabetes Mellitus
IVGTT	Intraveneous Glucose Tolerance Test
NIDDM	Non-insulin Dependent Diabetes Mellitus
NMM	New Minimal Model
OGTT	Oral Glucose Tolerance Test
OMM	Original version of Minimal Model
ORC	Observability Rank Criterion
RSS	Residual Sum of Squares
SDLN	Standard Deviation for the Log-Normal Distribution
SLI	Structurally Locally Identifiable
SGI	Structurally Globally Identifiable
SIA	Structural Identifiability Analysis
WHO	World Health Organization

Chapter 1

Introduction

Diabetes is a disease affecting many thousands of individuals worldwide. The population of diabetes sufferers is rising and will continue to rise rapidly in the future [WHO and IDF, 2006; Zimmet et al., 2001]. Much clinical research has been carried out to help improve, manage and control the condition of diabetes sufferers, to prevent the disease, to slow down the number of affected individuals by the disease [Boutayeb and Chetouani, 2006].

Today, mathematical modelling has been applied widely and has become inseparable from medical and clinical settings. Modellers are constantly finding new ideas and developments to incrementally improve and effectively manage, control and improve the condition of diabetes sufferers and even to prevent the number of sufferers worldwide [Boutayeb and Chetouani, 2006; Carson and Cobelli, 2001].

The basic idea of modelling is to transform a process into a mathematical set of equations, when any appropriate validated model can then be used to describe a real physiological system, for example the process of a clinical treatment. The development of a robust, valid and verified model allows its users to further understand, describe, explain and observe a physiological

system, e.g. test hypotheses and measure inference, estimating parameters, determine the sensitivity of a system, simulate and model both simple and complex experimental design [Cobelli and Carson, 2001].

The difficulty in modelling lies with the complexity of the physiological system under analysis. As physiological systems normally consist of a series of connectivities through the existence of nonlinear, stochastic and time-varying effects, involving different levels of the hierarchy of molecules, cells, organs and organisms and in most cases, the measurements obtained generally do not directly give information on the targeted subject. However, a valid model will allow life scientists to estimate the best time to perform blood sampling for optimal results [Cobelli and Carson, 2001]. Thus with the aid of modelling, the need for and level of experimentation on life subjects can potentially be reduced.

Over the years, different models have been designed and developed for various purpose and practices for treating and controlling diabetes. For example, there are models developed for the purpose of diabetes prevention, understanding glucose-insulin dynamics and kinetics, managing and controlling diabetes, managing complications caused by diabetes, cost-effectiveness of dealing with diabetes, and estimating populations of diabetes sufferers [Boutayeb and Chetouani, 2006].

Glucose-insulin dynamics models have been popularly used for the study of a better understanding of diabetes and glucose-insulin dynamics and kinetics. A valid and verified model may provide useful information on individuals or groups of subjects through appropriate clinical scenarios or experiments, for example the rate of glucose disappearance, insulin sensitivity, glucose sensitivity and missing or unobtainable information from clinical experiments [Bergman et al., 1979; Bergman and Bowden, 1981; Bergman et al., 1981; Picchini et al., 2005]. All of these models include unknown parameters that are

normally estimated from patient data.

Structural identifiability analysis is pre-requisite for mathematical models, to determine if all the unknown parameters within a model can be uniquely determined through noise-free input-output knowledge of the system. A structural indistinguishability analysis is performed to find out if two candidate models for the same process are distinguishable from one another given identical experimental output. These analyses are important and should essentially be performed on models prior to any fitting to experimental data.

This thesis focuses on the structural identifiability analyses of a selection of well known and new models for glucose-insulin dynamics. These glucose-insulin models play an important role for a better understanding of glucose-insulin metabolism through appropriate experiments, e.g. an Intravenous Glucose Tolerance Test (IVGTT), or Euglycemic Hyperinsulinemic Clamp (EIC) and glucose clamp experiment. The parameters in glucose-insulin dynamics models are commonly estimated using IVGTT and glucose clamp data sets.

Chapter 2 includes a brief background and literature review of diabetes and introduces the glucose-insulin dynamics models studied in this thesis. These models include the well-cited glucose-insulin dynamics model and so called Minimal Model (MM) [Bergman et al., 1979; Bergman and Bowden, 1981]; an Euglycemic Hyperinsulinemic Clamp (EIC) model [Picchini et al., 2005, 2006]; two modified versions of the Minimal Model, a Closed-loop Minimal Model (CLMM) and a Double-Pole in Closed-Loop Minimal Model (DPCLMM) [Arundel et al., 2010].

Chapter 3 includes the background theory and different approaches that can be used for structural identifiability analysis, i.e. the Taylor Series approach [Pohjanpalo, 1978], the Similarity Transformation approach and a recent variant [Vajda et al., 1989; Evans et al., 2002, 2005]; and a reparameterisation procedure [Chappell and Gunn, 1998] for an unidentified model (model

with parameters which is not uniquely identifiable from available input-output information). An introduction to parameter estimation and the computational packages used is also included in this chapter. Lastly, Chapter 3 includes an approach for performing a structural indistinguishability analysis of two non-linear models given identical experimental output.

Chapter 4 provides the structural identifiability analyses for the MM. Due to the complexity of the model structure, the structural identifiability of the MM is carried out in 3 parts: the original version of the MM and the extended version of the MM (EMM) over two phases, before and after glucose concentration reaches a glucose threshold. This chapter will then demonstrate parameter estimates obtained from one of the versions of the MM using certain sets of IVGTT data made available for this research project.

Chapter 5 provides similar analyses for the EIC model; Chapter 6 for the CLMM; and Chapter 7 for the DPCLMM. For some of the models, the structural identifiability analyses are performed using more than one approach as no conclusive result can be drawn from certain of the approaches applied. A reparameterisation procedure is also applied to one of the glucose-insulin models as the model is shown to be structurally unidentifiable, where the reparameterised model has a reduced number of parameters and is at least locally identifiable (in fact shown to be uniquely identifiable).

Chapter 8 shows the structural indistinguishability analysis of the MM and the CLMM as the CLMM is a modified version of MM and therefore these two models have similar model structure. The analysis is to determine whether these two models can be distinguished from each other through the same observations, i.e. through the observation of glucose and insulin concentrations.

The main objective of this thesis is to determine the structural identifiability of different glucose-insulin dynamics models, i.e. two versions of the MM, the EIC model, the CLMM and the DPCLMM. The structural identifia-

bility analyses for these glucose-insulin models (including the MM which was first introduced in 1979), as far as the author is aware, have never been published before. As the structural identifiability analysis is a pre-requisite to any numerical analysis in the modelling process, therefore it is essential to carry out such an analysis in order to establish any 'missing' information on the system parameters and structure of these models. This analysis is particularly important for the MM, as it is widely referenced and used in practice to obtain information on parameters such as insulin sensitivity through a single IVGTT experiment. However, if any parameters prove to be unidentifiable through the structural identifiability analysis (i.e. it is not possible to determine the uniqueness of any parameter through the available input-output information under a perfect, noise free environment), then any subsequent numerical analysis or parameter estimation following that could be meaningless.

Chapter 2

Literature Background: Diabetes and Glucose-Insulin Models

2.1 Introduction

Diabetes is a disease caused by high blood sugar levels. When blood glucose increases, insulin is released almost instantly by the pancreas to maintain normal glucose levels. The cause of the high blood sugar levels is usually insufficient or no production of insulin, and in some cases the body does not respond to insulin production adequately, this is also known as insulin resistance. There are two main types of diabetes: Type 1 and Type 2 [Ekoé and Zimmet, 2001b; Harris and Zimmet, 1997].

Type 1 diabetes is caused by a disorder of the autoimmune system resulting in the damaging of pancreatic cells that produce insulin, leading to a dramatic reduction or loss of insulin production. It can affect individuals at any age and it often occurs in children [Ekoé and Zimmet, 2001b; Harris and Zimmet, 1997]. Some research has reported that, in recent years, the

prevalence of Type 1 diabetes has increased among young children and the age group of those affected is decreasing in years; this may be due to modern lifestyles, for example environmental and genetic changes, heavier birth weight, diet and nutritional factors, higher body mass index etc. [IDF, 2006]. Type 1 diabetes is also known as Insulin Dependent Diabetes Mellitus as it is not only maintained with a balanced diet and active physical exercise, but patients require daily insulin administration for survival, to avoid the development of ketoacidosis, coma and death [Ekoé and Zimmet, 2001b; IDF, 2006].

Type 2 diabetes affects 90% of the diabetes population around the world. Type 2 patients usually either have insufficient production of insulin in their body or suffer from insulin resistance. Type 2 diabetes is usually found in individuals older than 40 years [Ekoé and Zimmet, 2001b; Harris and Zimmet, 1997]. However, it is now also seen in children. Obesity is one of the highest risk factors for the development of Type 2 diabetes, however, it does not imply that all obese individuals are diabetic or will be diabetic. Other causes and factors of Type 2 diabetes include genetically triggered, ethnicity, being overweight, high blood pressure, cardiovascular conditions, polycystic ovary syndrome or gestational diabetes in women, inactive physical lifestyles, excessive diet, alcohol and smoking. Sufferers are required to monitor and control their blood sugar level with a lifestyle of healthy diet and regular physical activity, and in some cases, medication and/or insulin are also used to help maintain low blood glucose levels. In very few cases, some Type 2 patients require insulin for survival, therefore, Type 2 is also known as Non-insulin Dependent Diabetes Mellitus [Ekoé and Zimmet, 2001b; IDF, 2006; Sincree et al., 2010].

Diabetes can be diagnosed and confirmed with a relatively simple and inexpensive blood test and with the existence of symptoms, e.g. thirst, frequent urination, weight loss etc. In many cases, patients are diagnosed with

pre-diabetes conditions, where blood glucose is higher than normal but lower than diabetic levels. Approximately 70% of pre-diabetes patients develop Type 2 diabetes later in life. However, patients can delay the onset of diabetes or regain normal blood glucose levels through appropriate lifestyle and careful monitoring of the condition. Pre-diabetes is also known as borderline diabetes, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) [Ekoé and Zimmet, 2001b; IDF, 2006].

For diabetes sufferers, regular tests are required for controlling blood glucose, foot problems, blood lipid and screening for retinopathy and kidney disease. Further tests are often required to obtain more accurate information such as insulin sensitivity, e.g. Oral Glucose Tolerance Test (OGTT), Intravenous Glucose Tolerance Test (IVGTT) and Euglycemic Hyperinsulinemic Clamp (EIC). Currently, there is no cure for diabetes. Patients are advised to make lifestyle changes and closely monitor their blood glucose levels and take appropriate medication accordingly, to reduce symptoms and prevent or delay the onset of other complications. Intensive insulin therapy is, however, required for Type 1 patients for survival [Ekoé and Zimmet, 2001b; IDF, 2006].

Diabetes is a serious condition and currently more than 285 million and 344 million individuals in the world are known to suffer from diabetes and pre-diabetes, respectively, and this figure is expected to rise up to 439 million for diabetes and 472 million for pre-diabetes by 2030 [Sincree et al., 2010]. The population of diabetes sufferers is now also increasing, even in developing countries, and it is also found in younger children. These phenomena would be preventable if the public was more aware of the risk factors of the disease and by simply altering their lifestyle to reduce the chances of developing diabetes. Diabetes often leads to serious complications such as cardiovascular disease, stroke, renal failure, neuropathy, foot ulcers, blindness, retinopathy, polyneuropathy, increased risk of infection and death, etc., even if treated [Clausen

et al., 1996; IDF, 2006; Sincree et al., 2010; WHO and IDF, 2006].

The study of diabetes, pre-diabetes, glucose-insulin pathology and related subjects has therefore become increasingly important within the fields of medicine, biology and pharmaceutics to find better solutions to improve and control the condition of diabetes and pre-diabetes patients, as well as to reduce the numbers suffering from this preventable situation.

2.2 Insulin Sensitivity

Insulin sensitivity is one of the key parameters for diabetes patients as it determines how well glucose disappears and glucose production is suppressed after insulin is released, or the level of insulin resistance in patients. It can be used to study and compare outcomes among groups of different individuals, ethnicity, species and between genders [Bergman, 2007].

A simple blood test is used to determine the blood glucose level of an individual and whether they are non-diabetic, pre-diabetic or diabetic. It does not directly provide insulin sensitivity information for patients. Therefore, further tests such as an OGTT, IVGTT and EIC are often used to obtain further, more comprehensive information [WHO, 1999; WHO and IDF, 2006].

In brief, an OGTT involves taking a dose of glucose and blood sampling is performed following this dose to determine the glucose disappearance from the system. However, the test occasionally fails due to variations in gastric emptying time and intestinal absorption. The problems could be avoided by applying an IVGTT [Lozner et al., 1941; WHO, 1999].

An IVGTT involves a bolus injection of glucose to raise the glycemic level of an individual followed by frequent blood sampling to provide information on the glucose disappearance in the blood hence providing the ability to observe the glucose clearance within the system [Caumo et al., 2001].

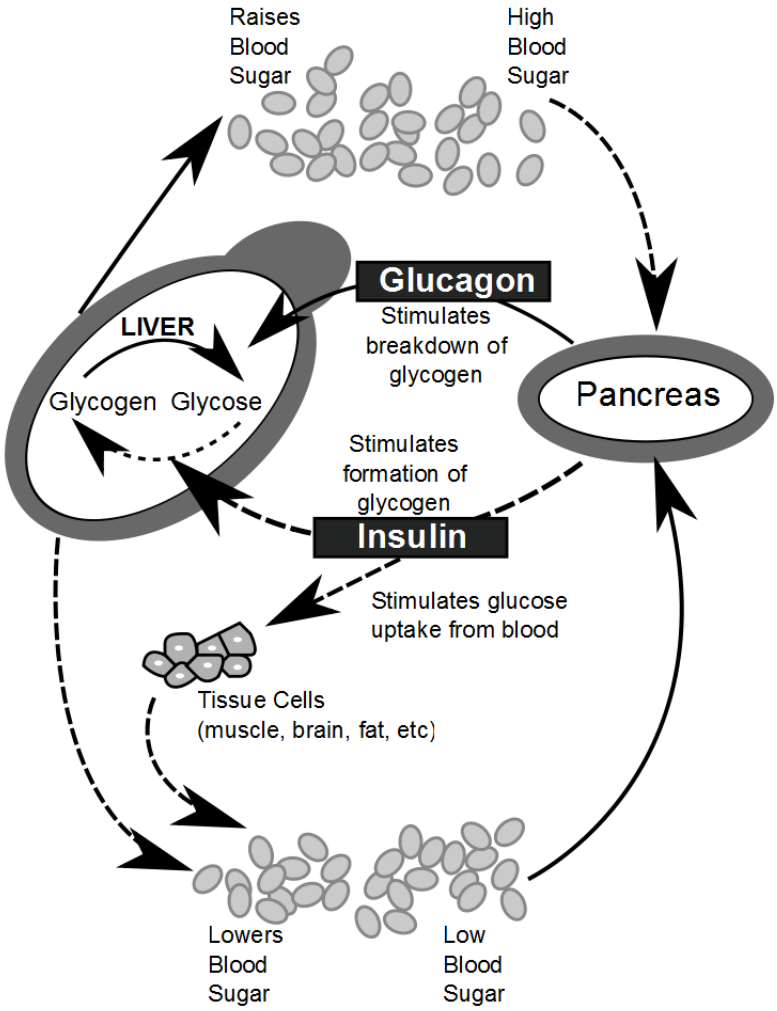

Figure 2.1: Insulin is produced and required for cells to use blood sugar and to lower blood glucose when it is raised. Diabetic patients suffer from insufficient or no production of insulin, or insulin resistance. [IDF, 2006]

Diabetes	
Fasting plasma glucose	$\geq$ 7.0 mmol/l (126mg/dl)
	or
2h plasma glucose*	$\geq$ 11.1 mmol/l (200mg/dl)
Impaired glucose tolerance (IGT)	
Fasting plasma glucose	< 7.0mmol/l (126mg/dl)
	and
2h plasma glucose*	$\geq$ 7.8 and <11.1 mmol/l
	(140mg/dl and 200mg/dl)
Impaired fasting glucose (IFG)	
Fasting glucose glucose	6.1 - 6.9 mmol/l (110 - 125mg/dl)
	and (if measured)
2h plasma glucose*	<7.8 mmol/l (140mg/dl)

*Venous plasma glucose 2h after ingestion of 75g oral glucose load
*If 2h plasma glucose is not measured, status is uncertain as diabetes or IGT cannot be excluded

Table 2.1: Recommended diagnostic criteria for diabetes and pre-diabetes [WHO and IDF, 2006]

The EIC was first introduced by DeFronzo et al. [1979] and it has since been widely applied and considered as the "gold standard" for measuring insulin sensitivity in humans and animals. This test involves infusing a variable dose of glucose to maintain a certain level of raised blood glucose during a course of insulin infusion. Through the observation of glucose uptake, this technique quantifies the whole-body tissue sensitivity to insulin under near steady state conditions for both glucose and insulin levels [DeFronzo et al., 1979; Vogel et al., 2006].

Table 2.1 shows the recommended values for diagnosis of diabetes and pre-diabetes (impaired glucose tolerance and impaired fasting glucose) using OGTT [WHO and IDF, 2006]. If an individual has a glucose concentration over 7.0mmol/l after fasting; or over 11.1mmol/l after 2 hours of ingestion of 75g of glucose load, there is a high possibility that they are suffering from diabetes. It is recommended by the International Diabetes Federation to take

two blood samples, i.e. at fasting and 2 hours after glucose load, to distinguish whether the individual is suffering from diabetes or pre-diabetes.

2.3 Mathematical Modelling

The common factor for all types of diabetes is hyperglycemia or high blood sugar [Ekoé and Zimmet, 2001a]. Blood sugar regulation is a complex system. When blood sugar levels increase, beta cells in the body are triggered for insulin production, and after certain enzyme-mediated chemical reactions, the blood sugar level is lowered to the normal level, see Figure 2.1, i.e. demonstrating the characterisation of a negative feedback control system [Cobelli and Carson, 2001]. However, glucose-insulin dynamics demonstrate the existence of a proportional and also derivative control system; insulin production takes place when glucose is raised, but also when the rate of glucose is increased [Carson et al., 2001].

The widely accepted glucose-insulin dynamics model, the Minimal Model (MM) was developed for predicting an insulin sensitivity index through OGTT or IVGTT while the subject is at rest [Bergman et al., 1979; Bergman and Bowden, 1981], Derouich and Boutayeb [2002] developed versions of a modified MM to predict and observe glucose-insulin levels during physical exercise, Picchini et al. [2005] have also developed models, and theirs are used to predict and describe glucose-insulin dynamics during EIC tests. However, the glucose-insulin pathology is very complex and there has not yet been a single model developed that can comprehensively and accurately describe and predict the complete glucose-insulin behaviour for an individual subject to multiple different scenarios.

The modelling of glucose-insulin dynamics began a few decades ago. The first published model was by Himsworth and Kerr [1939] to measure in-

sulin concentration *in vivo*. A simple model with two ordinary differential equations was then introduced by Bolie [1961] to estimate glucose disappearance and to study glucose-insulin dynamics. However, the real beginning of the modelling of glucose-insulin dynamics started after the introduction of the most cited model, the MM by Bergman et al. [Bergman et al., 1979]. The authors initially proposed seven different models, linear and nonlinear, each of them able to provide certain levels of information through data obtained from IVGTT. The best model (out of the seven models) was chosen and referred to as "The Minimal Model" because it satisfied the authors' requirements, to describe the glucose disappearance during the time course of an IVGTT and insulin sensitivity. As an extension of the original Minimal Model developed in 1979, Bergman and Bowden [1981] introduced an additional insulin equation to describe insulin behaviour.

Both versions of the MM, the original and extended versions, have since become the most cited and referenced in the literature for glucose-insulin dynamics. There are around 900 references to the MM over a cursory search [Bergman, 2007]. The MM has been a real inspiration for mathematical modellers in glucose-insulin dynamics as many models have been developed based on the principles of the MM, and also modified versions of the MM were developed for other clinical scenarios, for example Derouich and Boutayeb [2002] introduced a glucose-insulin dynamics model for physical exercise based on the MM; Caumo and Cobelli [1993] developed the New Minimal Model (NMM), which consists of two glucose compartments, in order to provide a better insight into the glucose dynamics.

There are numerous models available for OGTT and IVGTT with different variations. However, glucose-insulin dynamics models for clamp-related experiments are limited. Picchini and colleagues introduced possibly the first verified model to describe glucose-insulin dynamics during the time course

of an EIC experiment in 2005 [Picchini et al., 2005]. The model consists of two versions, deterministic and stochastic. Picchini and co-authors [Picchini et al., 2005] are among the pioneers in terms of stochastic modelling and have successfully demonstrated the advantages of stochastic modelling for clamp experiment data [Picchini et al., 2005, 2006, 2008].

Most models published so far have received not only good reviews, but also criticism [Boutayeb and Chetouani, 2006]. The extended Minimal Model is reported to function in two steps, i.e. it is not a fully integrated system. De Gaetano and Arino [2000a,b] then introduced an improved Minimal Model which overcomes the common problem, i.e. that the MM is physiologically unrealistic and that the system is unstable. However, De Gaetano and Arino's model was reported to consist of an unrealistic specific term by [Li et al., 2000] and the authors therefore introduced another model with slight modification which overcomes this issue.

There are many more models for diabetes covering different aspects, some of them need further improvement and some not. The most important thing is that a model is valid and verified in term of structurally (*a priori*) and numerically (*posteriori*) identifiability before it is used for practical application.

The two most classic forms of MM will be studied and analysed in this thesis as they are the most-cited mathematical models in almost 900 publications. [Bergman, 2007]. In addition, a model developed to describe the EIC experiment [Picchini et al., 2006] is also studied, tested and analysed as it is, as far as the author is aware, the first glucose-insulin dynamics model developed to cater primarily for clamp experiments. Lastly, modified versions of the MM, a Closed-Loop Minimal Model and a Double-Poled Closed-Loop Minimal Model developed by Arundel et al. [2010] are studied as these models appear to have the ability to provide representation of the glucose-insulin

pathology over a complete IVGTT experiment and also describe both glucose-insulin dynamics for an IVGTT simultaneously.

2.4 The Minimal Model

The Minimal Model (MM) [Bergman et al., 1979; Bergman and Bowden, 1981] is one of the most referenced glucose-insulin dynamics model. It was first published by Bergman and colleagues in 1979 [Bergman et al., 1979] and it marked the real beginning of the mathematical modelling of glucose-insulin dynamics. Professor Bergman was awarded the Banting Medal by the American Diabetes Association in year 2006 for his achievement in diabetes research [Bergman, 2007].

Bergman and colleagues [Bergman et al., 1979] published a paper proposing seven mathematical models to simulate the glucose disappearance during the time course of an IVGTT aiming that one of the models proposed would provide a clearer understanding of glucose-insulin dynamics, glucose disappearance and be able to estimate the insulin sensitivity of a targeted subject, e.g. a diabetes patient or a healthy individual. Of all these models, model VI was ultimately considered as most appropriate and has since been referred to as the "Minimal Model" by the authors, and by many other researchers [Bergman et al., 1979]. The model will be referred to as the "Original Minimal Model" (OMM) in this text for the ease of comparison with different forms of Minimal Model which will be introduced later in this chapter.

The authors [Bergman et al., 1979] stated that the model predicts the glucose disappearance after the injection of glucose throughout the process of the IVGTT, and that the four parameters within the model are establishable and with similar parameter values for a subject, the model could be used in simulation to predict experimental outcomes. The OMM also provides

information about the quantitative insulin sensitivity index which can be determined from the ratio of two model parameters and this information can be obtained simply from a single glucose injection [Bergman et al., 1979]. Table 2.2 shows the parameter values emerged from the OMM for different groups of individuals, i.e. normal individuals, IGT patients and Type 2 Diabetes patients.

The diagrammatic version of the OMM is shown in Figure 2.2 and the system equations for the OMM are commonly seen in the following form [Bergman et al., 1979]:

$$\dot{G}(t) = -(p_1 + X(t))G(t) + p_1 G_b \tag{2.1}$$

$$\dot{X}(t) = -p_2 X(t) + p_3(I(t) - I_b) \tag{2.2}$$

and the initial conditions are given by

$$G(0) = G_0 \tag{2.3}$$

$$X(0) = 0 \tag{2.4}$$

$$I(0) = I_0 = I_b + p_7 \tag{2.5}$$

where

$G(t)$	(mmol/L) denotes the glucose concentration
$X(t)$	(min^{-1}) denotes the concentration of remote plasma insulin
$I(t)$	(mU/L) denotes the time course of plasma insulin
G_b	(mmol/L) denotes the basal level of glucose concentration
I_b	(mU/L) denotes the basal level of insulin concentration
p_1	(min^{-1}) denotes rate constant of glucose "mass action"
p_2	(min^{-1}) denotes the rate constant which explains the ability of spontaneous decrease of tissue glucose uptake

Parameter	Normal	IGT	Type 2 Diabetes
S_G	0.021 ± 0.008	0.016 ±0.007	0.015 ± 0.001
S_I	2.62 ± 2.21	1.27 ± 1.20	0.57 ± 0.82
S_G (min^{-1}) represents glucose effectiveness			
S_I ($\times 10^{-4}$ min^{-1} per μU/ml) represents the insulin sensitivity			

Table 2.2: Physiological parameters emerging from the Minimal Model [Haffner et al., 1996, 1997; Bergman, 2007]

p_3 (min^{-2} $(\text{mU/L})^{-1}$) denotes the ability of the insulin-dependent increase in tissue glucose uptake,

p_7 (mU/L) denotes the plasma insulin concentration at time $t = 0$

One of the reasons this particular model structure is chosen is because this model is closer to the physiological system than the six other models proposed in the paper, and that it includes the insulin inhibition of hepatic glucose balance, therefore providing useful information such as a precise formulated description of the insulin sensitivity index S_I [Bergman et al., 1979]. Moreover, unknown parameters can be numerically estimated under precision indicated by the authors, and the values estimated for the parameters are realistic in physiological terms, and most importantly, the model is able to simulate the glucose-insulin dynamics with the minimum number of parameters.

In addition this model is able to predict the glucose-insulin kinetics after the application of a bolus glucose injection, via an IVGTT. The model is also able to provide information on glucose effectiveness. Bergman et al. [1979] defined the insulin sensitivity index based on the following definitions:

The *glucose effectiveness* of an individual can be described as the quantitative enhancement of glucose disappearance in response to the rise in plasma glucose concentration and *insulin sensitivity* at steady state is the quantitative influence of insulin to increase the enhancement of glucose disappearance [Bergman et al., 1979]. This is based on the basic definition of glucose ef-

fectiveness and insulin sensitivity and therefore yields the insulin sensitivity index (S_I) given by [Bergman et al., 1979]:

$$S_I = \frac{p_3}{p_2} \, . \tag{2.6}$$

The units of S_I are expressed in $\text{min}^{-1}/(\mu\text{U/ml})$ (fractional glucose disappearance per insulin concentration unit), and this is the ratio of two of the system parameters. This index represents the sensitivity of the periphery to insulin and also the sensitivity of the liver to inhibit hepatic glucose production [Bergman et al., 1979]. Bergman et al. [1979] also provides for further information on how the insulin sensitivity index can be determined.

The sensitivity index for the OMM varies according to subjects, and relies on the glucose disappearance as a function of insulin in plasma, but the plasma glucose concentration allows the users to compare subjects of different body size, weight and composition [Bergman et al., 1979].

This model was claimed to be identifiable, i.e. all the unknown parameters are identifiable [Bergman et al., 1979]. However, many researchers might have misunderstood what type of identifiability [Bergman et al., 1979] addressed. The OMM was in fact numerically tested and based on the idea of the fractional standard deviation of the fitted data as Bergman et al. [1979] stated that *"We considered a parameter to be nonidentifiable if the fractional standard deviation of the parameter estimates (when fitting a single experiment) exceeded 100%."*. Therefore, the authors only published results on numerical identifiability of the OMM in [Bergman et al., 1979], and did not test structurally identifiability of the model.

The OMM has been modified and extended with an additional equation to describe insulin concentration during the course of an IVGTT experiment

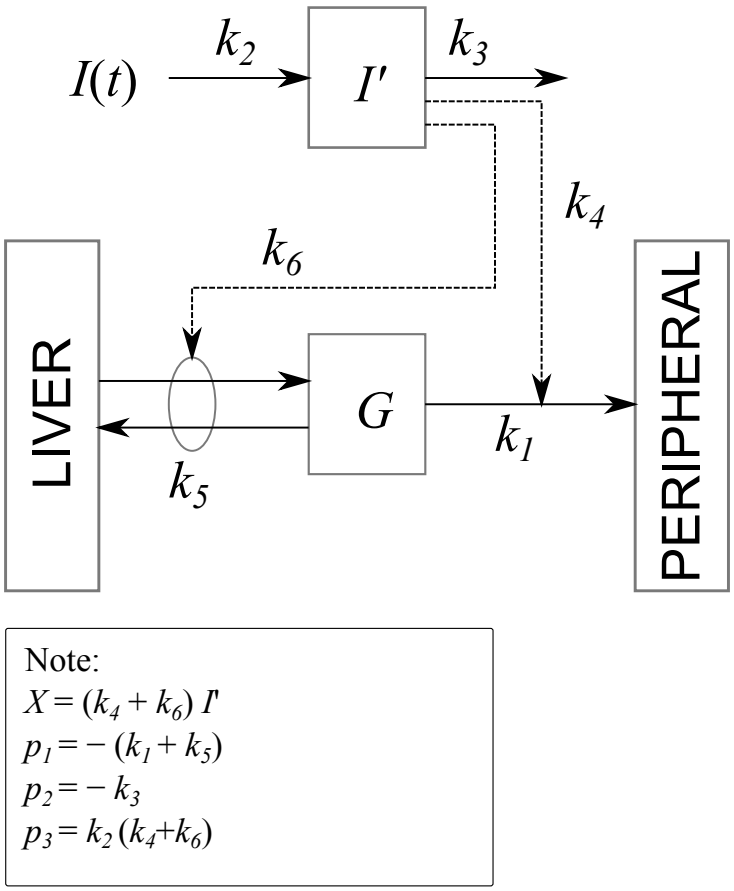

Figure 2.2: The diagrammatic version of the OMM; referred to as Model VI. [Bergman et al., 1979]

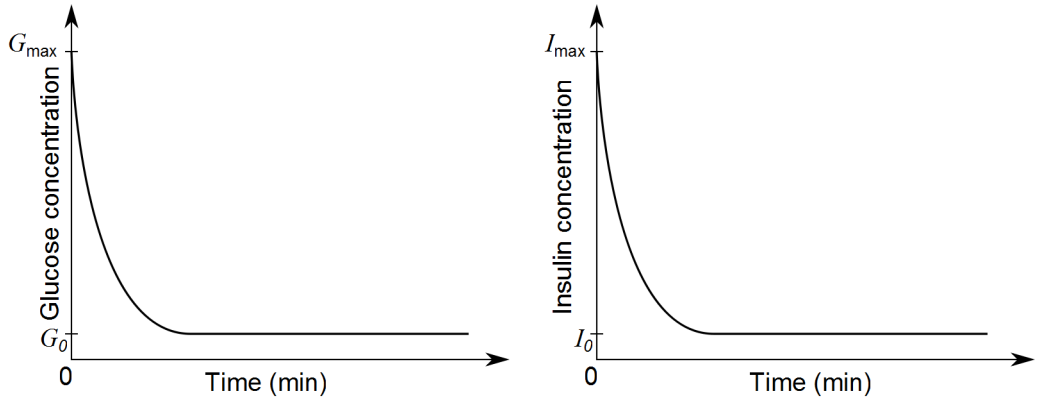

Figure 2.3: The EMM captures the second-phase glucose-insulin kinetics where the initial conditions of the EMM are when glucose and insulin concentrations are at their peak.

[Bergman and Bowden, 1981]:

$$\dot{I}(t) = p_4 t[G(t) - p_5] - p_6[I(t) - I_b], \; G(t) > p_5, \tag{2.7}$$

$$\dot{I}(t) = -p_6[I(t) - I_b], \qquad G(t) < p_5. \tag{2.8}$$

These insulin equations are developed to describe the second-phase insulin kinetics, as shown in Fig. 2.3. Combining with the OMM, the system equations of the Extended Minimal Model (EMM) in their now commonly considered standard form are given by Bergman and Bowden [1981]; Boutayeb and Chetouani [2006]; De Gaetano and Arino [2000a] as the following:

$$\dot{G}(t) = -[p_1 + X(t)]G(t) + p_1 G_b \tag{2.9}$$

$$\dot{X}(t) = -p_2 X(t) + p_3[I(t) - I_b] \tag{2.10}$$

$$\dot{I}(t) = p_4 t[G(t) - p_5] - p_6[I(t) - I_b], \; G(t) > p_5, \tag{2.11a}$$

$$\dot{I}(t) = -p_6[I(t) - I_b], \qquad G(t) < p_5, \tag{2.11b}$$

and the initial conditions are given by

$$G(0) = G_0 \tag{2.12}$$

$$X(0) = 0 \tag{2.13}$$

$$I(0) = I_0 = p_7 + I_b \tag{2.14}$$

where

$G(t)$ (mmol/L) denotes the plasma glucose concentration

$I(t)$ (mU/L) denotes the plasma insulin concentration

$X(t)$ (min^{-1}) is a function describing the insulin excitable tissues responding to glucose uptake

G_b (mmol/L) denotes the plasma glucose concentration at basal level

I_b (mU/L) denotes the plasma insulin concentration at basal level

p_1 (min^{-1}) denotes the rate constant of glucose "mass action"

p_2 (min^{-1}) denotes the rate constant which explain the ability of spontaneous decrease of tissue glucose uptake

p_3 (min^{-2} $(\text{mU/L})^{-1}$) denotes the ability of the insulin-dependent increase in tissue glucose uptake

p_4 ($(\text{mU/L})(\text{mmol/L})^{-1}$ min^{-1}) denotes the second phase release of insulin, which also describes the pancreatic sensitivity

p_5 (mmol/L) denotes the threshold of plasma glucose concentration which the second-phase insulin secretion is stimulated by glucose

p_6 (min^{-1}) denotes the rate constant of insulin disappearance

p_7 (mU/L) denotes the plasma insulin concentration at time $t = 0$

This form of the MM is possibly one of the most referenced glucose-insulin models. Like the OMM, it is commonly used to measure glucose disappearance effectiveness and insulin sensitivity from plasma glucose and insulin through the glucose disappearance from an experiment IVGTT. As shown previously, the OMM consists of only two equations, Eqns. (2.1) and (2.2). Therefore, the OMM is a subset of the EMM.

The insulin differential equation consists of two parts, and describes two different insulin behaviours based on the value of glucose concentration. Eqn. (2.11a) describes the pre-switching phase, when insulin is due to glucose above a threshold level p_5, e.g. after a meal or instantly after a bolus injection of glucose for an IVGTT. The value of the glucose threshold, parameter p_5, is close to the glucose basal level. The term $p_4 t(G(t) - p_5)$ in Eqn. (2.11a), given enough time, grows linearly with time and will eventually lead to instability of the system. Toffolo et al. [1980] explained that the multiplication by the time term (t) in Eqn. (2.11a) defines the rate of insulin secretion by the pancreas and the rate of insulin clearance in response to hyperglycemic distribution within the system [Toffolo et al., 1980]. Arundel et al. [2010] commented that a term like $p_4 t(G(t) - p_5)$ can require replacement by a decaying exponential term to ensure system stability.

The post-switching phase Eqn. (2.11b) describes the decay of insulin in the body after the insulin action has successfully decreased the blood glucose below the threshold level (i.e. $G(t) < p_5$) [Bergman et al., 1979; Bergman and Bowden, 1981], when the time term is "switched-off". It is believed that this quite rare and interesting mathematical structure has limited the application of the MM to certain tests (i.e. it is not normally applicable to clamp experiments). The term $p_4 t(G(t) - p_5)$ in Eqn.(2.11a) creates a switch or discontinuity (i.e. the system equation is piecewise continuous) and, due to its structure, also provides a possible reason for its lack of universal application. It has been

reported that the OMM and EMM are limited to estimating OGTT and/or IVGTT data [Boutayeb and Chetouani, 2006], and glucose clamp data have seldom, if ever, been used successfully in association with this model form.

De Gaetano and Arino [2000a] carried out a formal study of the qualitative behaviour of the EMM, including the steady state of the model, and reported that when the basal glucose level is above the pancreatic target glucose level, 'the model equations give rise to unbounded solutions', and when basal glucose level is below the pancreatic target glucose level, 'no equilibrium solution can be obtained', causing the insulin action concentration to rise without bounds infinitely [De Gaetano and Arino, 2000a].

The structural identifiability analysis, a prerequisite analysis essential for all system modelling prior to any parameter fitting, has not been carried out for both OMM and EMM when the models were introduced (as far as the author is aware).

A structural identifiability analysis was performed on a model close in form to the OMM, the "New Minimal Model" (NMM) [Caumo and Cobelli, 1993]. The model consists two glucose compartments and a remote insulin compartment. The structural identifiability analysis of the NMM is carried out using the Taylor Series expansion approach of Pohjanpalo [Pohjanpalo, 1978] and the result shows that the model is globally identifiable (i.e. all the parameters are uniquely determinable) under certain physiological conditions that, at steady state, the insulin-independent glucose disposal is three times insulin-dependent glucose disposal [Caumo and Cobelli, 1993; Saccomani et al., 2001b; Caumo et al., 2001]. The diagramamatic version of the NMM is shown in Figure 2.4 and the system equations for the NMM are given by [Caumo and

Cobelli, 1993]

$$\dot{q}_1^*(t) = -\left(k_p + \frac{F_{01}}{V_1 g(t)} + k_{21}\right) q_1^*(t) + k_{12} q_2^*(t) \qquad q_1(0) = D \qquad (2.15)$$

$$\dot{q}_2^*(t) = -(k_{02} + x^*(t) + k_{12}) q_2^*(t) + k_{21} q_1^*(t) \qquad q_2^*(0) = 0 \qquad (2.16)$$

$$\dot{x}^*(t) = -k_b x^*(t) + k_a(i(t) - i_b) \qquad x^*(0) = 0 \qquad (2.17)$$

$$g(t) = \frac{q_1^*(t)}{V_1} \qquad (2.18)$$

where q_1^* and q_2^* are the tracer masses in the two glucose compartments; V_1 is the volume of the accessible compartment, k_p, k_{12}, k_{21} and k_{02} are constant rate parameters and k_a and k_b describe insulin action with the same meaning as p_2 and p_3 in the OMM, and variables $g(t)$, $x^*(t)$ and $i(t)$ are equivalent to $G(t)$, $X(t)$ and $I(t)$ respectively in the OMM . The function $i(t)$ represents insulin as a forcing term or input to the model. The NMM does not include a differential equations for insulin (Eqn. (2.11a) and Eqn. (2.11b)), like the OMM. After substituting parameters $k_a = p_2$ and $k_b = p_3$ and variables equivalent to the OMM, and rearranging yield

$$\dot{G}(t) = -\frac{1}{V_1}\left(k_p + \frac{F_{01}}{V_1 G(t)} + k_{21}\right) q_1^*(t) + k_{12} q_2^*(t)/V_1 \qquad q_1(0) = D \qquad (2.19)$$

$$\dot{q}_2^*(t) = -(k_{02} + X(t) + k_{12}) q_2^*(t) + k_{21} q_1^*(t) \qquad q_2^*(0) = 0 \qquad (2.20)$$

$$\dot{X}(t) = -p_2 X(t) + p_3(I(t) - I_b) \qquad X(0) = 0 \qquad (2.21)$$

Comparing the mathematical structure of the NMM, Eqns. (2.19) - (2.21) to the OMM, it is clear that the two models have different mathematical structures. Therefore, the structural identifiability of the NMM does not necessarily imply that the OMM and the EMM are also identifiable.

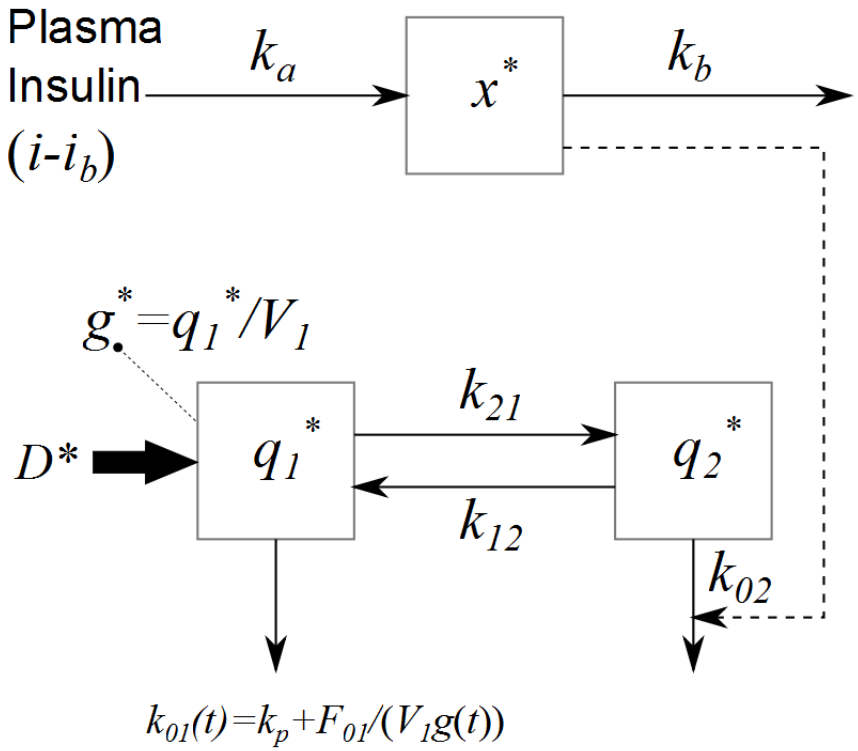

Figure 2.4: Diagrammatic version of the NMM. The model consists of two glucose compartments [Caumo and Cobelli, 1993].

2.5 Euglycemic Hyperinsulinemic Clamp Model

As the name suggests, this model was developed to study the glucose-insulin reactions to a Euglycemic Hyperinsulinemic Clamp (EIC). It expresses the oscillations generated due to the response to glucose and insulin infusions at different (constant) rates. The model can be used to determine the insulin resistance behaviour analytically. The application of the EIC model allows its users to recover further information from clamp data, allowing the comparison of insulin resistance between different subject groups, e.g. obese and non-obese individuals. The unknown parameters within the model are estimated with respect to typically available clamp data, and the model is known to be numerically identifiable [Picchini et al., 2005, 2006].

The diagrammatic version of the EIC model is given in Figure 2.5 and the system equations for this model are given by the following [Picchini et al., 2005, 2006]:

$$\dot{G}(t) = \frac{T_{gx}(t-\tau_g) + T_{gh}(t)}{V_g} - \frac{T_{xg}G(t)}{0.1 + G(t)} - K_{xgI}G(t)I(t) \tag{2.22}$$

$$\dot{I}(t) = \frac{T_{iG}G(t) + T_{ix}(t)}{V_i} - K_{xi}I(t) \tag{2.23}$$

where

$$T_{gh}(t) = T_{ghmax}\exp(-\lambda G(t)I(t)) \tag{2.24}$$

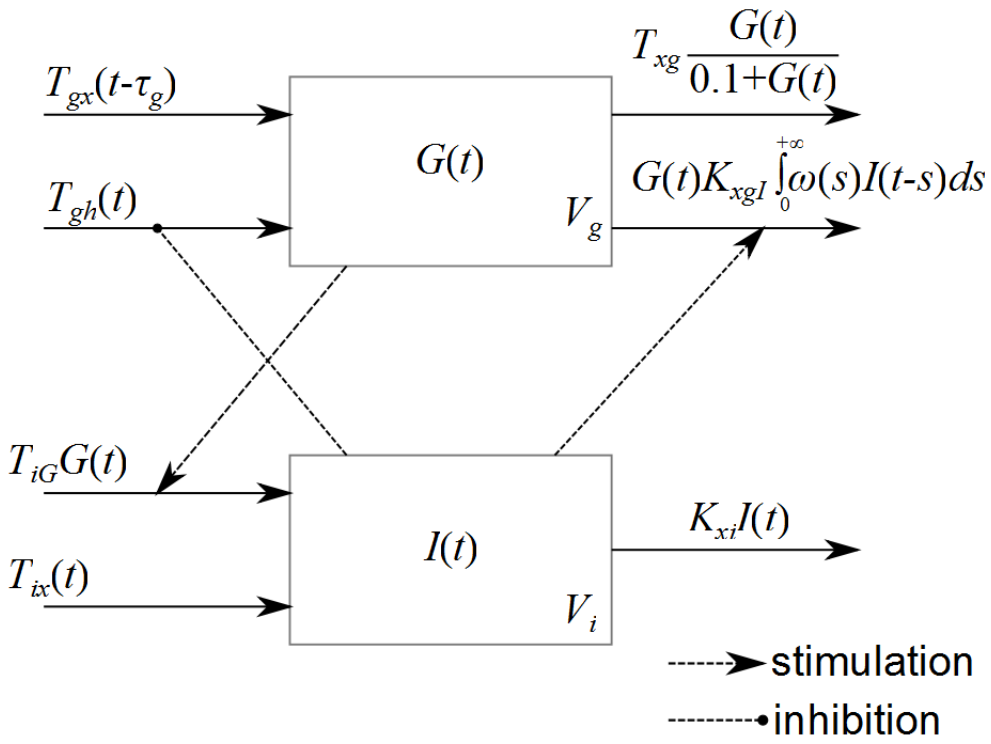

Figure 2.5: Diagrammatic version of the EIC Model. [Picchini et al., 2005]

and the initial conditions are given by

$$T_{gh}(0) = T_{ghb} = T_{ghmax} \exp -\lambda G_b I_b \tag{2.25}$$

$$G(0) = G_b \tag{2.26}$$

$$I(0) = I_b \tag{2.27}$$

where

$T_{gx}(t)$ (mmol/min/kg) denotes the glucose infusion rate at time t

$T_{ix}(t)$ (pmol/min/kg) denotes the insulin infusion rate at time t

$T_{gh}(t)$ (mmol/min/kg) denotes the concentration of Hepatic Glucose Output at time t

T_{ghmax} (mmol/min/kg) denotes the maximal Hepatic Glucose Output at zero glucose and insulin concentration

G_b	(mM) denotes the basal glycemia
I_b	(pM) denotes the basal insulinemia
τ_g	(min) denotes the time delay in glycemia due to glucose infusion
V_g	(L/kg) denotes the volume distribution of glucose
V_i	(L/kg) denotes the volume distribution of insulin
T_{xg}	(mM/min) denotes the rate constanat of the maximal insulin-independent for glucose tissue uptake
K_{xgI}	(min^{-1}/pM) denotes the insulin-dependent apparent first-order rate constant for glucose tissue uptake at insulinemia $I(t)$
K_{xi}	(min^{-1}) denotes the rate constant of first order and insulin removal from plasma
T_{iG}	(mU/min/mM) denotes the apparent zero-order net insulin synthesis rate at unit glycemia
T_{ghb}	(mmol/min/kg) denotes the basal level of T_{gh}
λ	($\text{mM}^{-1}\text{pM}^{-1}$) denotes the rate constant for Hepatic Glucose Output decrease with increase of glycemia and insulinemia.

A EIC is the key experiment for determining the insulin sensitivity of a subject or an individual and is also referred to as the "gold standard" for measuring insulin sensitivity [DeFronzo et al., 1979; Vogel et al., 2006]. The experiment is however more complex and expensive to perform compared to an OGTT or IVGTT. The EIC model allows its users to study the glucose-insulin dynamics and behaviour during the course of a clamp experiment. Therefore, a structural identifiability analysis is important for such a model. Based on the observations of the parameter estimations for EIC model in [Picchini et al., 2005], the typical glucose-insulin dynamics for EIC are shown in Figure 2.6.

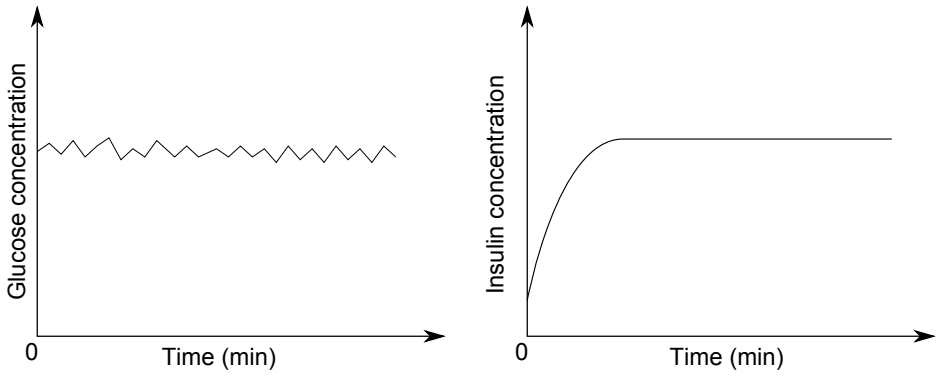

Figure 2.6: A typical glucose-insulin dynamics for EIC.

2.6 Closed-Loop Minimal Model

A modified version of EMM, Closed-Loop Minimal Model (CLMM), introduced by Arundel et al. [2010] is also considered in this thesis as it is believed to overcome the instability issue of the system equation for insulin concentration within the EMM. Besides, the CLMM also includes first phase insulin behaviour (as shown in Figure 2.7) within the system and the time term (t) from the EMM is now replaced by an exponential term, allowing the system parameters to be estimated simultaneously, with no switch involved, and still remains a good representation of the glucose-insulin pathology compared to the EMM. The system equations for the CLMM are given by

$$\dot{G}(t) = -(p_1 + k_6 I_R(t))G(t) + p_1 G_b \tag{2.28}$$

$$\dot{I}_R(t) = k_2(I(t) - I_b) - p_2 I_R(t) \tag{2.29}$$

$$\dot{I}(t) = M_1(G(t) - h)e^{-\lambda t} + \gamma(G(t) - h) - p_{exit} I(t) \tag{2.30}$$

where

$G(t)$ (mg/L) denotes the glucose concentration at time t

$I(t)$ (mU/L) denotes the insulin concentration at time t

$I_R(t)$ (min $^{-1}$) denotes the new remote insulin 'action' at time t

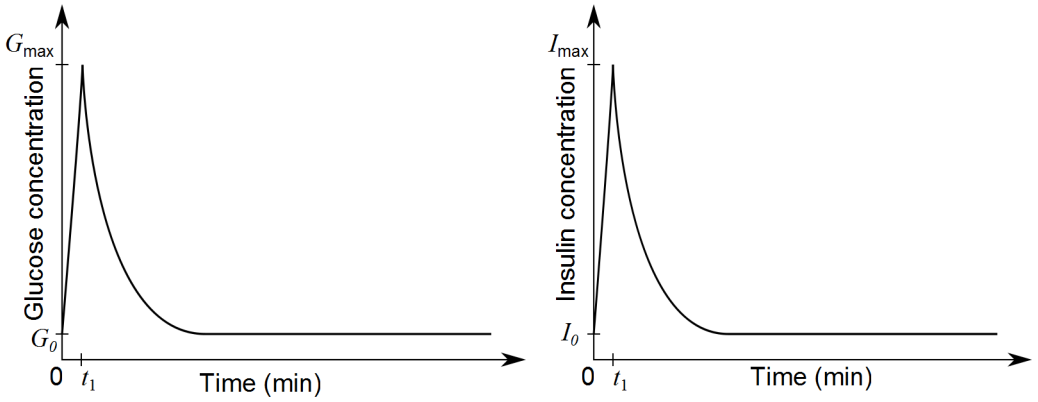

Figure 2.7: The CLMM and DPCLMM capture the first-phase of glucose-insulin kinetics, where at time $t = 0$, glucose and insulin concentrations are at G_0 and I_0, and first phase kinetics are generated with a single impulsive glucose input. Glucose and insulin concentrations are at their peak at t_1

p_1	(min^{-1}) denotes the rate constant of glucose "mass action"
p_2	(min^{-1}) denotes the rate constant which explain the ability of spontaneous decrease of tissue glucose uptake
γ	($\text{mU mmol}^{-1}\ \text{min}^{-2}$) denotes the second phase release of insulin, which also describes the pancreatic sensitivity
h	(mmol/L) denotes the threshold plasma glucose concentration which the second-phase insulin secretion is stimulated by glucose
p_{exit}	(min^{-1}) denotes the rate constant of insulin disappearance
M_1	denotes a rate constant
λ	denotes a rate constant of the exponential term

The remote insulin action $X(t)$ of the OMM and EMM is now replaced by $I_R(t)$ which is used to control glucose kinetics directly whereby [Arundel et al., 2010]

$$X(t) = k_6 I(t). \tag{2.31}$$

Figure 2.8 shows the diagrammatic version of the CLMM. The diagram shows

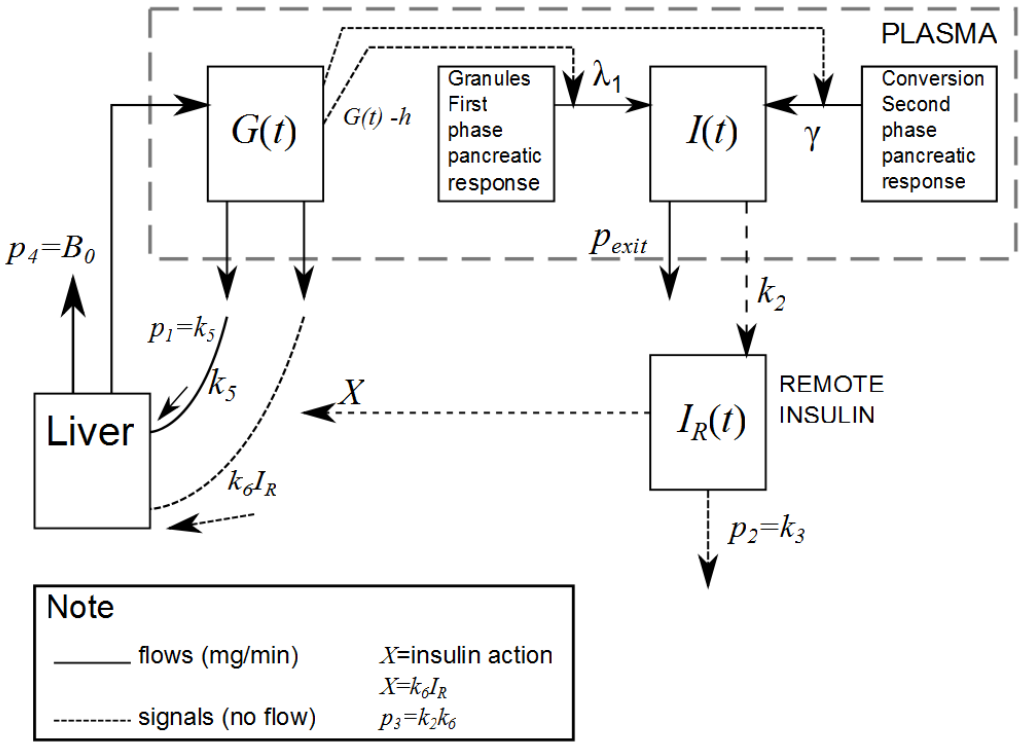

Figure 2.8: Diagrammatic version of the CLMM [Arundel et al., 2010]

the compartment $I_R(t)$ as the 'remote' aspect of the insulin action $X(t)$ [Arundel et al., 2010]. Arundel et al. [2010] report that the model has produced an improved fit to a set of IVGTT data originally published in Pacini and Bergman [1986].

2.7 Double-Pole in Closed-Loop Minimal Model

The Double-Pole Closed-Loop Minimal Model (DPCLMM) is a modified version of CLMM introduced by Arundel et al. [2010]. The DPCLMM is slightly different in terms of structure compared to the CLMM; the diagrammatic version of the DPCLMM is given in Figure 2.9. The model has an additional double-pole for the second-phase glucose-controller path. The model considers a two-compartment catenary system, and includes a double-pole term of

the form $te^{-p_1 t}$ which provides a delay in the glucose-insulin dynamics with the inclusion of a possible 'remote' glucose pool. The differential equation for insulin includes two decaying exponentials to ensure stability of the system [Arundel et al., 2010].

The DPCLMM is a modified version of the EMM, with a reproduction of the glucose-insulin plasma concentration profiles, along with the remote insulin profile, and a double-pole added to the second-phase glucose-controller path in a closed-loop form [Arundel et al., 2010]. The DPCLMM has the ability to simulate periods of sustained insulin concentration during the time course of insulin, stably falling back to a basal insulin level, and it also explains the 'time' factor incorporated in the EMM in an alternative and mathematical smooth manner, without losing physiological realism. In addition, the model is claimed to provide better fit to a set of IVGTT experimental data (published in Pacini and Bergman [1986]) compared to the EMM and CLMM [Arundel et al., 2010]. Like the CLMM, the DPCLMM is able to generate the first phase glucose-insulin dynamics of IVGTT experiments as shown in Figure 2.7.
The system equations of the DPCLMM is given by

$$\dot{G}(t) = -(p_1 + k_6 I_R(t))G(t) + p_1 G_b \tag{2.32}$$

$$\dot{I}_R(t) = k_2(I(t) - I_b) - p_2 I_R(t) \tag{2.33}$$

$$\dot{I}(t) = M_1(G(t) - h)e^{-\lambda t} + \gamma(G(t) - h)te^{-p_1 t} - p_{exit} I(t) \tag{2.34}$$

where

$G(t)$ (mg/L) denotes the glucose concentration at time t

$I(t)$ (mU/L) denotes the insulin concentration at time t

$I_R(t)$ (min $^{-1}$) denotes the new remote insulin 'action' at time t

p_1 (min^{-1}) denotes the rate constant of glucose "mass action"

p_2 (min^{-1}) denotes the rate constant which explain the ability of spontaneous decrease of tissue glucose uptake

γ ($mU\ mmol^{-1}\ min^{-2}$) denotes the second phase release of insulin, which also describes the pancreatic sensitivity

h (mmol/L) denotes the threshold plasma glucose concentration which the second-phase insulin secretion is stimulated by glucose

p_{exit} (min^{-1}) denotes the rate constant of insulin disappearance

M_1 denotes a rate constant

λ denotes a rate constant of the exponential term

γ denotes a scaling parameter.

The DPCLMM has only recently been introduced and published in Arundel et al. [2010]; the structural identifiability of this model has not previously been considered.

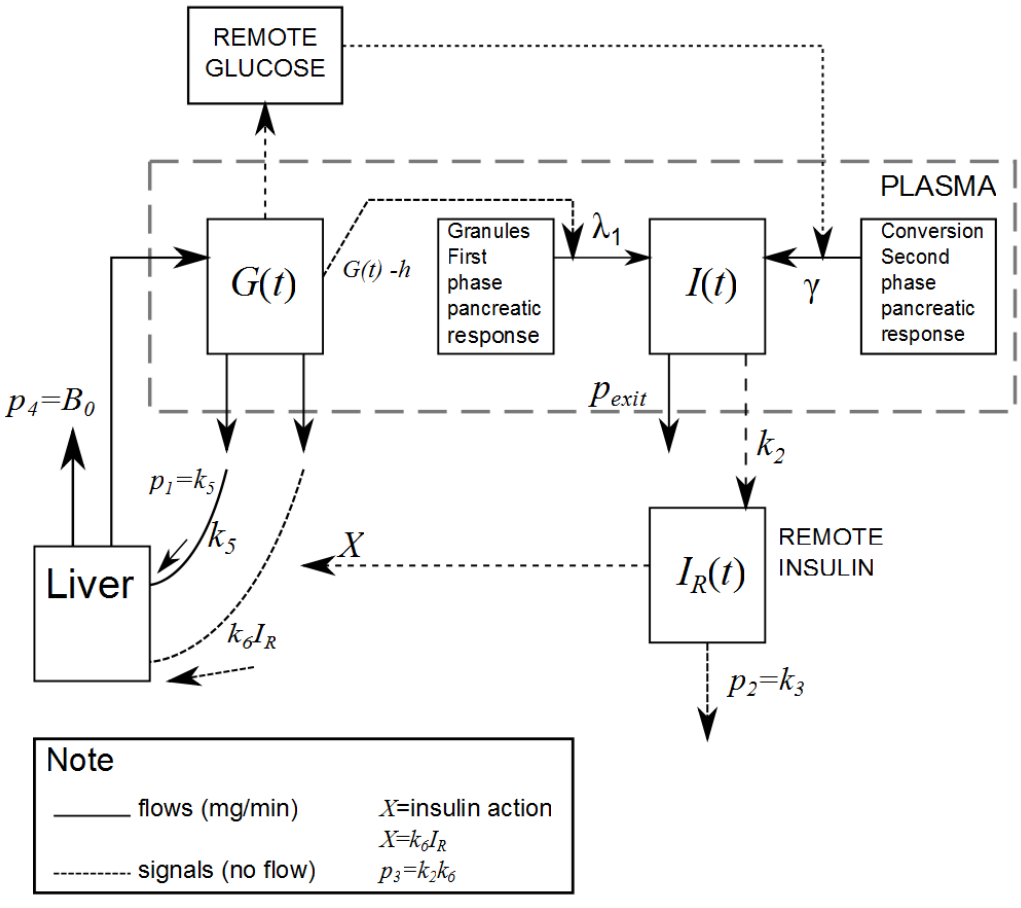

Figure 2.9: Diagrammatic version of the DPCLMM [Arundel et al., 2010]

Chapter 3

Background Theory: Identifiability of Models

3.1 Structural Identifiability Analysis

A mathematical model usually includes parameters, some known, some unknown which need to be identified from appropriate experimental data. It is extremely important that modellers are confident that they are able to identify and determine all the unknown parameters within a model through the experimental data available, such as data collected from blood sampling, for any subsequent predictions to be meaningful. The question of whether a model is well-presented, correctly describing the real system is determined by whether modellers are able to use the data available to obtain and estimate a unique set of solutions for the unknown parameters [Cobelli and DiStefano, 1980; Jacquez, 1999; Saccomani et al., 2001b].

Structural identifiability arises from the inverse problem of inferring from the known, or assumed, properties of a system of suitable model structure and estimates for the corresponding rate constants and other parameters. Structural identifiability analysis considers the uniqueness of the unknown

model parameters from the input-output structure corresponding to proposed experiments to collect data for parameter estimation, under an assumption of the availability of perfect, noise-free data. The existence of noise-free data is assumed for *a priori* (non-numerical) structural identifiability analysis purposes.

If any of the parameters are unidentifiable, the model is also structurally unidentifiable and to solve this problem, additional data or information is required. If no further information can be obtained then the complexity of the model must be reduced in some appropriate way, or the input-output structure of the system must be redesigned. The redesign of an unidentifiable model involves changing the function of input and/or output in order to provide a globally or locally identifiable model [Evans et al., 2002]. Evans and Chappell [2000] show a method to generate a local identifiability of a system from unidentified system with the method of reparameterisation [Evans and Chappell, 2000].

However, modellers must be clear that a structurally globally identifiable model does not guarantee good parameter estimation from experimentally obtained data; and in many cases an *a priori* identifiability analysis could be difficult or tedious to perform, especially for complex models. These are however, not reasons for not performing the analysis [Saccomani et al., 2001b].

This is why a structural identifiability analysis is a required pre-requisite to any experimental design, numerical parameter estimation or system identification even and it must be carried out prior to any numerical identification, particularly in biological and physiological systems where unknown parameters have physical significance. A model cannot be assumed to be structurally globally identifiable if all of the unknown parameters can be estimated numerically through computer software almost unconditionally; modellers often tend to neglect *a priori* analysis due to the use of modern computer software for

fitting [Jacquez, 1999; Saccomani et al., 2001b].

Besides that, structural identifiability analysis plays an important role in establishing the superiority of the model, whether the input-output information is sufficient to enable unique estimation for the parameters [Saccomani et al., 2001b]. The analysis helps modellers to decide which models are worth working with, and those that not worth wasting time on and simply cannot produce any reasonably useful outcome [Saccomani et al., 2001b].

In actual fact, the most important objective of performing structural identifiability analysis is to find out whether any unknown parameters present within the postulated model are unidentifiable from the observations available on the system. This is particularly important for those parameters or combinations of parameters that have practical significance. Under such circumstances if any parameters are unidentifiable, under perfect, noise free conditions, then any subsequent estimation of these parameters from data with the presence of noise would prove meaningless. Moreover, an analysis of an error-free or noise-free model is purely structural [Cobelli and DiStefano, 1980; Jacquez, 1999].

Structural identifiability analysis is therefore an important, but often overlooked, theoretical prerequisite to experimental design, system identification and parameter estimation. If parameters estimated are to be used to inform about intervention or inhibition strategies, or other critical decisions, then it is essential that all parameters be uniquely identifiable.

The methods most commonly applied that are available for structural identifiability analysis for linear systems include the Laplace transform/transfer function approach, the Taylor series approach and the Similarity Transformation (exhaustive modelling) approach; and for nonlinear systems include the Taylor series approach, the differential algebra approach, the Similarity Transformation approach and variations [Cobelli and DiStefano, 1980; Evans et al.,

2002; Godfrey and DiStefano, 1987; Margaria et al., 2001; Pohjanpalo, 1978; Saccomani et al., 2001a,b; Vajda et al., 1989].

It is difficult to predict which approach or method requires the least effort for a particular model and therefore it is worth trying more than one approach for satisfactory results [Godfrey and DiStefano, 1987]. In many cases, the aid of symbolic computational tools is necessary, especially for complex models, as analysis by hand even for a linear but complex system could be difficult [Chappell et al., 1990]. Mathematical modellers, with minimum knowledge on performing *a priori* analysis, may prefer using a computer software tool, such as DAISY (Differential Algebra for Identifiability of System), to test for parameter identifiability using differential algebra algorithms and these are suitable for testing for both linear and nonlinear systems with polynomial or rational state space equations [Bellu et al., 2007].

3.1.1 General Methods and Definitions

The idea of general structural identifiability analysis considers a system with the following structure [Vajda et al., 1989]:

$$\begin{aligned} \dot{\boldsymbol{x}}(t,\boldsymbol{p}) &= \boldsymbol{f}(\boldsymbol{x}(t,\boldsymbol{p}),\boldsymbol{p}) + \boldsymbol{u}(t)\boldsymbol{g}(\boldsymbol{x}(t,\boldsymbol{p}),\boldsymbol{p}) \\ \boldsymbol{x}(0,\boldsymbol{p}) &= \boldsymbol{x}_0(\boldsymbol{p}) \\ \boldsymbol{y}(t,\boldsymbol{p}) &= \boldsymbol{h}(\boldsymbol{x}(t,\boldsymbol{p}),\boldsymbol{p}) \end{aligned} \tag{3.1}$$

where $\boldsymbol{x}(t,\boldsymbol{p}) \in \mathbb{R}^n$ denotes the state vector of model variables; $\boldsymbol{y}(t,\boldsymbol{p}) \in \mathbb{R}^m$ denotes the state vector of system output; vector $\boldsymbol{x}_0$ is the initial condition vector for the state variables; vector $\boldsymbol{u}(t) \in \boldsymbol{U}[0,t_1]$ is the set of bounded and measureable inputs on the time interval $0 \leq t \leq t_1$; $\boldsymbol{p} \in \Omega$ is the (q dimensional) vector of unknown parameters, where Ω denotes the set of possible parameter values, $\Omega \subset \mathbb{R}^m$ is the feasible parameter space and q denotes the

number of parameters; vector y is the output vector. The smooth functions $\boldsymbol{f}(\cdot,\cdot)$ and $\boldsymbol{h}(\cdot,\cdot)$ are nonlinear in the state variables $\boldsymbol{x} \in \mathbb{R}^n$, the input $\boldsymbol{u}(t)$ and parameter vectors $\boldsymbol{p} \in \Omega$.

For any generic parameter vector $\boldsymbol{p} \in \Omega$ then each parameter p_i is said to be *locally identifiable* if there exists a neighbourhood of vectors around p, denoted by $N(\boldsymbol{p})$, such that if $\bar{\boldsymbol{p}} \in N(\boldsymbol{p}) \subseteq \Omega$ and for every input $\boldsymbol{u}(t)$ for $t \geq 0$,

$$\boldsymbol{y}(\cdot, \boldsymbol{p}) = \boldsymbol{y}(\cdot, \bar{\boldsymbol{p}}) \tag{3.2}$$

implies $\bar{p}_i = p_i$ (i.e. there are a countable number of possible solutions of Eqn. (3.2) for the unknown parameter p_i).

The parameter p_i is *globally/uniquely identifiable* if, $N(\boldsymbol{p}) = \Omega$ (i.e. each parameter has only a unique solution from Eqn. (3.2)) and p_i is *unidentifiable* if it is not locally identifiable (i.e. there is no such neighbourhood $N(\boldsymbol{p})$ and there are an infinite number of solutions for each parameter from Eqn. (3.2)) [Chappell et al., 1990; Evans et al., 2002].

The model (3.1) is said to be *structurally globally/uniquely identifiable* if all of its unknown parameters p_i are globally/uniquely identifiable, *structurally locally identifiable* if all of its unknown parameters p_i are locally identifiable and at least one of its parameters is *not* globally identifiable and *unidentifiable* if at least one of its unknown parameters p_i is unidentifiable [Chappell et al., 1990; Evans et al., 2002].

In a practical sense, the existence of perfect, noise-free data is unrealistic. Real experimental data can include both system and/or observational noise and may cause a uniquely identifiable model in the structural sense to become numerically unidentifiable. In particular, and in general, when data contain a high noise component, then less information can be obtained from them. When observational noise is added to the system, the output, (3.2)

becomes

$$\boldsymbol{y}(t,\boldsymbol{p}) = \boldsymbol{h}(\boldsymbol{x}(t,\boldsymbol{p}),\boldsymbol{p}) + \boldsymbol{\epsilon}(t) \tag{3.3}$$

where $\boldsymbol{\epsilon}(t)$ represents the noise, $\boldsymbol{h}(\boldsymbol{x}(t,\boldsymbol{p}),\boldsymbol{p})$ represents the perfect output. The noisy system is now considered as non-unique [Cobelli and DiStefano, 1980; Hengl et al., 2007]. The analysis of the model including noise, is therefore *a posteriori*.

A parameter is *practically identifiable* if the parameter is uniquely identifiable with a small standard deviation [Hengl et al., 2007]. *A posteriori* (non-structural or numerical) identifiability analysis usually follows the *a priori* stage and involves fitting the mathematical model to a set (or sets) of experimental data in order to numerically determine a unique value for each unknown parameter with a high degree of confidence.

3.1.2 Taylor Series Approach

The Taylor Series Approach [Pohjanpalo, 1978] is commonly used for experiments involving an impulsive input, where u is a single input. The output of the models and their time derivatives are evaluated in terms of the parameters $\boldsymbol{p}$ at a known time point, very often at the initial conditions $t = 0^+$. Since the coefficients of the Taylor Series are unique, the identifiability problem is therefore reduced to determining the number of solutions in a set of nonlinear algebraic equations in the parameters [Evans and Chappell, 2000; Vajda et al., 1989]. The Taylor Series expansion of the observation $\boldsymbol{y}(t,\boldsymbol{p})$ is given by

$$\boldsymbol{y}(t,\boldsymbol{p}) = \boldsymbol{y}(0^+,\boldsymbol{p}) + \boldsymbol{y}^{(1)}(0^+,\boldsymbol{p})t + \boldsymbol{y}^{(2)}(0^+,\boldsymbol{p})\frac{t^2}{2} + ... + \boldsymbol{y}^{(i)}(0^+,\boldsymbol{p})\frac{t^i}{i!} + ..., \tag{3.4}$$

where

$$\boldsymbol{y}^{(i)}(0^+, \boldsymbol{p}) \equiv \frac{d^i \boldsymbol{y}}{dt^i}(\tau, \boldsymbol{p}), \quad i = 0, 1, 2, ... \tag{3.5}$$

Using this approach for nonlinear systems may be difficult, as it is not yet possible to determine a strict/tight upper bound on the number of equations/coefficients required for a particular system. For a nonlinear system, the analysis approach includes [Pohjanpalo, 1978; Chappell et al., 1990]:

1. Successive differentiation of $\boldsymbol{y}(t, \boldsymbol{p})$.

2. Evaluation of $\boldsymbol{y}^{(i)}(0^+, \boldsymbol{p})$ by substitution of quantities already known from $\boldsymbol{y}(0^+, \boldsymbol{p})$ and lower derivatives ($< i$).

3. A test on the independence of the equations in the successive derivatives and on what parameters, if any can be identified at each stage of differentiation.

Therefore, for a nonlinear system, this approach can only determine if a parameter is uniquely identifiable if the solution is unique and that the model is globally identifiable if all the parameters are uniquely identifiable. If not all the parameters are uniquely identifiable it does not imply that the model is not globally identifiable (the approach is necessary, but not sufficient).

3.1.3 Similarity Transformation Approach

The Similarity Transformation approach or exhaustive modelling approach for nonlinear system is introduced by Vajda et al. [1989] and is based on the local state isomorphism theorem [Hermann and Krener, 1977; Isidori, 1985; Vajda and Rabitz, 1989].

The system (3.1) is considered. Let M represent a connected open subset of $\mathbb{R}^n$ such that $\boldsymbol{x} \in M$; it is assumed that $\boldsymbol{f}(\cdot, \boldsymbol{p})$ and $\boldsymbol{g}(\cdot, \boldsymbol{p})$ are real analytic on M for all $\boldsymbol{p} \in \Omega$, where Ω represents the set of possible parameter

values, that is, a connected open set in $\mathbb{R}^q$, where q represents the number of parameters.

The controllability and observability of the models must also be established for the nonlinear model before the structural identifiability analysis can take place [Vajda et al., 1989]. To establish the Controllability Rank Criterion (CRC), let $X(M)$ represent the set of all C^∞ vector fields defined on M and that the element of $X(M)$ is the n-dimensional column vector-valued functions of $\boldsymbol{x} \in M$. Therefore, $X(M)$ is a vector space and also a Lie algebra, with Lie bracket operation given by [Vajda et al., 1989]

$$[\boldsymbol{\varphi}_1, \boldsymbol{\varphi}_2](\boldsymbol{x}) \triangleq \frac{\partial \boldsymbol{\varphi}_2}{\partial \boldsymbol{x}} \boldsymbol{\varphi}_1(\boldsymbol{x}) - \frac{\partial \boldsymbol{\varphi}_1}{\partial \boldsymbol{x}}(\boldsymbol{x}) \boldsymbol{\varphi}_2(\boldsymbol{x}) \tag{3.6}$$

where $\boldsymbol{\varphi}_1$, $\boldsymbol{\varphi}_2$ and $[\boldsymbol{\varphi}_1, \boldsymbol{\varphi}_2] \in X(M)$.
The vector field $\boldsymbol{\varphi}_i(\boldsymbol{x})$ is given by

$$\boldsymbol{\varphi}^i(\boldsymbol{x}) \triangleq \boldsymbol{f}(\boldsymbol{x}) + \boldsymbol{u}^i \boldsymbol{g}(\boldsymbol{x}). \tag{3.7}$$

where $\boldsymbol{u}^i$ is a piecewise constant control.
Then $\boldsymbol{\varphi}^i \in X(M)$. An element of $\boldsymbol{F}(\boldsymbol{x})$ has the following form [Vajda et al., 1989]:

$$\Big[\varphi^1, \big[\varphi^2, [\cdots, [\varphi^{i-1}, \varphi^i], \cdots]\big]\Big] \tag{3.8}$$

whereby F^0 is a subset of $X(M)$ and is closed under the multiplication of the Lie bracket. System (3.1) is said to satisfy the Controllability Rank Criterion (CRC) at $\boldsymbol{x}_0$ if F^0 has dimension equal to n [Hermann and Krener, 1977; Vajda et al., 1989].

To establish the Observability Rank Criterion (ORC) of a nonlinear system (3.1), let $\boldsymbol{h}$ represent the output function and h_j the jth-component of $\boldsymbol{h}$. Then $\boldsymbol{h} \in C^\infty$, where $C^\infty(M)$ is the real vector space. The Lie derivative

of h_j along the vector field $\boldsymbol{\varphi}^i \in X(M)$ is given by [Vajda et al., 1989]

$$L_{\varphi^i}(\boldsymbol{h})(\boldsymbol{x}) \equiv \frac{\partial \boldsymbol{h}(\boldsymbol{x})}{\partial \boldsymbol{x}} \boldsymbol{\varphi}^i(\boldsymbol{x}) \tag{3.9}$$

where the gradient is given by

$$d\boldsymbol{h} = \frac{\partial \boldsymbol{h}}{\partial \boldsymbol{x}} \tag{3.10}$$

and

$$d\boldsymbol{h}(\boldsymbol{x}) = \left[\frac{\partial h(\boldsymbol{x})}{\partial x_1}, \cdots, \frac{\partial h(\boldsymbol{x})}{\partial x_n} \right]. \tag{3.11}$$

The Lie derivative, after rearranging, is given by

$$L_{\varphi^i}(h_j)(\boldsymbol{x}) \triangleq \frac{\partial h_j}{\partial \boldsymbol{x}}(\boldsymbol{x}) \varphi^i(\boldsymbol{x}). \tag{3.12}$$

Let $\mathcal{G}^0$ be the subset of $C^\infty(M)$ consisting of and $h_1, h_2, ..., h_m$ where $\mathcal{G}$ is the smallest linear subspace of $C^\infty(M)$ containing $\mathcal{G}^0$ that is closed with respect to Lie differentiation along the elements of $\mathcal{F}^0$. An element of $\mathcal{G}$ therefore has the following structure

$$L_{\varphi_1}\Big(... \big(L_{\varphi^i}(h_j) \big) ... \Big) \tag{3.13}$$

and it is verified that $\mathcal{G}$ is closed under Lie differentiation along the elements of $\mathcal{F}$. Thefore, $d\mathcal{G}$ has the form of

$$d\Bigg(L_{\varphi^1}\Bigg(L_{\varphi^{i-1}}\Bigg(..., \Big(L_{\varphi^i}\big(h(\boldsymbol{x}) \big) \Big), ... \Bigg) \Bigg) \Bigg). \tag{3.14}$$

Let $d\mathcal{G}(\boldsymbol{x})$ represent the space of vectors determined by evaluating the element of $d\mathcal{G}$ at $x \in M$. If the dimension of $d\mathcal{G}$ is n, then system (3.1) is said to have fulfilled the Observability Rank Criterion (ORC) at $\boldsymbol{x}_0$ [Hermann and Krener, 1977; Vajda et al., 1989] .

The system (3.1) is said to be *locally reduced* at $\boldsymbol{x}_0 \in M$ if it satisfies both the CRC and ORC at $\boldsymbol{x}_0$ [Vajda et al., 1989].

Theorem 3.1.1. Assume that the model of (3.1) is *locally reduced* at $\boldsymbol{x}_0(\boldsymbol{p})$ for all $\boldsymbol{p} \in \Omega$. Consider the parameter values $\boldsymbol{p}$, $\tilde{\boldsymbol{p}} \in \Omega$, an open neighbourhood V of $\boldsymbol{x}_0(\tilde{\boldsymbol{p}})$ in M, and any analytical mapping $\lambda : V \to \mathbb{R}^n$ defined on $V \subset \mathbb{R}^n$ such that

$$\text{Rank } \frac{\partial \lambda(\tilde{\boldsymbol{x}})}{\partial \tilde{\boldsymbol{x}}} = n \qquad \text{for all } \tilde{\boldsymbol{x}} \in V \tag{3.15}$$

$$\lambda(\boldsymbol{x}_0(\tilde{\boldsymbol{p}})) = \boldsymbol{x}_0(\boldsymbol{p}) \tag{3.16}$$

$$\boldsymbol{f}(\lambda(\tilde{\boldsymbol{x}}, \boldsymbol{p}) = \frac{\partial \lambda(\tilde{\boldsymbol{x}})}{\partial \tilde{\boldsymbol{x}}} \boldsymbol{f}(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{p}}) \tag{3.17a}$$

$$\boldsymbol{g}(\lambda(\tilde{\boldsymbol{x}}, \boldsymbol{p}) = \frac{\partial \lambda(\tilde{\boldsymbol{x}})}{\partial \tilde{\boldsymbol{x}}} \boldsymbol{g}(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{p}}) \tag{3.17b}$$

$$\boldsymbol{h}(\lambda(\tilde{\boldsymbol{x}}, \boldsymbol{p}) = \boldsymbol{h}(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{p}}) \tag{3.17c}$$

for all $\tilde{\boldsymbol{x}} \in V$. Then there exists $t_1 > 0$ such that (3.1) is globally identifiable at $\boldsymbol{p}$ in the experiment $(\boldsymbol{x}_0(\boldsymbol{p}), U[0, t_1])$ if and only if conditions (3.15) - (3.17c) imply $\tilde{\boldsymbol{p}} = \boldsymbol{p}$.

3.1.4 Structural Identifiability Analysis for Autonomous Systems

When it comes to the analysis of an uncontrolled (autonomous) nonlinear system, an approach developed by Evans et al [Evans et al., 2002] motivated by the principle of the Similarity Transformation Approach is considered. This is based on the idea of testing the identifiability of rational system at $\boldsymbol{p} \in \Omega$. This approach uses the existence of a smooth mapping that connects the state trajectories of local-time indistinguishable parameter vectors. It also compares the existence of a state-isomorphism between locally reduced systems with indistinguishable input-output behaviour [Evans et al., 2002]. The uncontrolled

system consists of a similar form to model (3.1), except it has no input $\boldsymbol{u}(t)$ and the following form is considered [Evans et al., 2002]:

$$\begin{aligned} \dot{\boldsymbol{x}}(t,\boldsymbol{p}) &= \boldsymbol{f}(\boldsymbol{x}(t,\boldsymbol{p}),\boldsymbol{p}) \\ \boldsymbol{x}(0,\boldsymbol{p}) &= \boldsymbol{x}_0(\boldsymbol{p}) \\ \boldsymbol{y}(t,\boldsymbol{p}) &= \boldsymbol{h}(\boldsymbol{x}(t,\boldsymbol{p}),\boldsymbol{p}) \end{aligned} \tag{3.18}$$

where $\boldsymbol{p} \in \Omega$, an open subset of $\mathbb{R}^q$ is a constant parameter vector. It is assumed that $\boldsymbol{f}(\cdot,\cdot)$ and $\boldsymbol{h}(\cdot,\cdot)$ are rational functions (i.e., fractions of polynomials) in both $\boldsymbol{x}$ and $\boldsymbol{p}$. For all $\boldsymbol{p} \in \Omega$, denote by $M(\boldsymbol{p})$ the largest connected open subset of $\mathbb{R}^n$ containing $\boldsymbol{x}_0(\boldsymbol{p})$ such that both $\boldsymbol{f}(\cdot,\boldsymbol{p})$ and $\boldsymbol{h}(\cdot,\boldsymbol{p})$ are well-defined on $M(\boldsymbol{p})$, the largest connected open subset of $\mathbb{R}^n$ containing $\boldsymbol{x}_0(\boldsymbol{p})$ such that both $\boldsymbol{f}(\cdot,\boldsymbol{p})$ and $\boldsymbol{h}(\cdot,\boldsymbol{p})$ are well-defined on $M(\boldsymbol{p})$. Let $\tau(\boldsymbol{p})$ be the supremum of the set of all $\tau > 0$ such that $\boldsymbol{x}(t,\boldsymbol{p}) \in M(\boldsymbol{p})$ for $0 \leq t \leq \tau$. The output $\boldsymbol{y}(t,\boldsymbol{p}) \in \mathbb{R}^r$, and it is assumed that the initial condition vector $\boldsymbol{x}_0(\cdot)$ is a rational function in $\boldsymbol{p}$.

Definition 3.1.2. Parameter vectors $\boldsymbol{p}, \bar{\boldsymbol{p}} \in \Omega$ are said to be *local-time indistinguishable*, written $\boldsymbol{p} \sim \bar{\boldsymbol{p}}$, if there exists a $\tau > 0$ such that $\boldsymbol{y}(t,\boldsymbol{p}) = \boldsymbol{y}(t,\bar{\boldsymbol{p}})$ for all $t \in [0,\tau)$ [Evans et al., 2002].

Definition 3.1.3. A model for form (3.18) is said to be globally identifiable at $\boldsymbol{p} \in \Omega$ if $\bar{\boldsymbol{p}} \in \Omega$ and $\boldsymbol{p} \sim \bar{\boldsymbol{p}}$ imply that $\bar{\boldsymbol{p}} = \boldsymbol{p}$. If this is true on some neighbourhood of $\boldsymbol{p}$ then the model is locally identifiable at $\boldsymbol{p} \in \Omega$ [Evans et al., 2002].

Definition 3.1.4. If Eqn. (3.18) is globally (locally) identifiable at $\boldsymbol{p}$ for all $\boldsymbol{p} \in \Omega$, except for a subset of a closed set of (Lebesgue) measure zero, then it is said to be structurally globally (locally) identifiable. The model is said to be unidentifiable. The model is said to be unidentifiable if it is not structurally

locally identifiable [Evans et al., 2002].

Theorem 3.1.5. For $\boldsymbol{p} \in \Omega$, let $\mu_1, ..., \mu_n$ be smooth functions for which Eqn. (3.18) satisfies the ORC at $\boldsymbol{x}_0(\boldsymbol{p})$ and H the corresponding function defined as $H : (\boldsymbol{x}, \boldsymbol{p}) \mapsto (\mu_1(\boldsymbol{x}, \boldsymbol{p}), ..., \mu_n(\boldsymbol{x}, \boldsymbol{p}))^T$. If $\bar{\boldsymbol{p}} \in \Omega$, then $\boldsymbol{p} \sim \bar{\boldsymbol{p}}$ if and only if there exists a neighbourhood $V_{\bar{\boldsymbol{p}}}$ of $\boldsymbol{x}_0(\bar{\boldsymbol{p}})$, a $\tau > 0$ and a C^∞ map $\lambda : V_{\bar{\boldsymbol{p}}} \to M(\boldsymbol{p})$ such that [Evans et al., 2002]

$$H_p(\lambda(\boldsymbol{x})) = H_{\bar{p}}(\boldsymbol{x}) \tag{3.19}$$

For all $\boldsymbol{x} \in V_{\bar{\boldsymbol{p}}}$ and

$$\lambda(\boldsymbol{x}_0(\bar{\boldsymbol{p}})) = \boldsymbol{x}_0(\boldsymbol{p}) \tag{3.20}$$

$$\boldsymbol{f}(\lambda(\boldsymbol{x}(t, \bar{\boldsymbol{p}})), \boldsymbol{p}) = \frac{\partial \lambda}{\partial \boldsymbol{x}}(\boldsymbol{x}(t, \bar{\boldsymbol{p}}))\boldsymbol{f}(\boldsymbol{x}(t, \bar{\boldsymbol{p}})) \tag{3.21}$$

$$\boldsymbol{h}(\lambda(\boldsymbol{x}(t, \bar{\boldsymbol{p}})), \boldsymbol{p}) = \boldsymbol{h}(\boldsymbol{x}(t, \bar{\boldsymbol{p}}), \bar{\boldsymbol{p}}) \tag{3.22}$$

For all $t \in [0, \tau)$, where $\boldsymbol{x}(t, \bar{\boldsymbol{p}})$ is the solution of the system (3.18) for parameter vector $\bar{\boldsymbol{p}}$.

3.1.5 Confirmation of an Unidentifiable System

The method is a straightforward version of the Similarity Transformation approach for structural identifiability analysis by Evans et al. [2002] (see Section 3.1.4). It can be applied to prove and confirm that a model is indeed structurally unidentifiable. This method determines the parameters that are not unique for a given output. It does not completely characterise the equivalence classes of parameter vectors that are indistinguishable from the model output. However, a partition of these equivalence classes is generated which can enable the determination of some, or all, or any unidentifiable parameters [Evans et al., 2005].

Theorem 3.1.6. Suppose that the system (3.18) satisfies the ORC at $\boldsymbol{x}_0(\boldsymbol{p})$ for some $\boldsymbol{p} \in \Omega$, and let $H(\cdot,\cdot)$ denote the corresponding function defined via $H(\boldsymbol{x},\boldsymbol{p}) = (\theta_1(\boldsymbol{x},\boldsymbol{p}),...,\theta_n(\boldsymbol{x},\boldsymbol{p}))^T$. If $\bar{\boldsymbol{p}} \in \Omega$, then $\bar{\boldsymbol{p}} \sim \boldsymbol{p}$ if and only if there exists an open neighbourhood $V_{\bar{\boldsymbol{p}}}$ of $\boldsymbol{x}_0(\bar{\boldsymbol{p}})$, a $\tau > 0$, and a smooth map $\phi : V_{\bar{p}} \to M(\boldsymbol{p})$ such that [Evans et al., 2005]

$$H_p(\boldsymbol{\phi}(\boldsymbol{x})) = H_{\bar{\boldsymbol{p}}}(\boldsymbol{x}) \tag{3.23}$$

for all $\boldsymbol{x} \in V_{\bar{\boldsymbol{p}}}$ *and*

$$\boldsymbol{\phi}(\boldsymbol{x}_0(\bar{\boldsymbol{p}})) = \boldsymbol{x}_0(\boldsymbol{p}) \tag{3.24}$$

$$\boldsymbol{f}(\boldsymbol{\phi}(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),\boldsymbol{p}) = \frac{\partial \boldsymbol{\phi}}{\partial \boldsymbol{x}}(\boldsymbol{x}(t,\bar{\boldsymbol{p}}))\boldsymbol{f}(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) \tag{3.25}$$

$$\boldsymbol{h}(\boldsymbol{\phi}(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),\boldsymbol{p}) = \boldsymbol{h}(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) \tag{3.26}$$

For all $t \in [0,\tau)$ *where* $\boldsymbol{x}(t,\bar{\boldsymbol{p}})$ *is the solution of the system (3.18) for the parameter vector* $\bar{\boldsymbol{p}}$.

It is assumed that the system (3.18) satisfies the *Observability Rank Criterion* at $\boldsymbol{x}_0(\boldsymbol{p})$ such that $\boldsymbol{p} \in \boldsymbol{\Omega}$. Let $F(\boldsymbol{p})$ represent the subset of $\boldsymbol{p} \in \boldsymbol{\Omega}$, of all possible parameter vectors $\bar{\boldsymbol{p}}$ such that $\boldsymbol{\phi}$, defined in (3.23) satisfies Eqns. (3.24) - (3.25). The set $F(\boldsymbol{p})$ consists of precisely those parameter vectors that are indistinguishable from $\boldsymbol{p}$. If this set consists of $\boldsymbol{p}$ only, then the system (3.18) is globally identifiable at $\boldsymbol{p}$. The system is locally identifiable at $\boldsymbol{p}$ if there exists a neighbourhood $N(\boldsymbol{p})$ of $\boldsymbol{p}$ such that $F(\boldsymbol{p}) \cap N(\boldsymbol{p}) = \{\boldsymbol{p}\}$. These results are structural if they remain true for all parameter vectors $\boldsymbol{p}$ except possibly where the components of $\boldsymbol{p}$ satisfy some *a priori* algebraic equation(s) [Evans et al., 2005].

Remark 3.1.7. Considering only the sufficiency condition in Theorem 3.1.6: In the proof [Evans et al., 2005] the ORC is only used to construct a smooth

function $\boldsymbol{\phi}$ when $\bar{\boldsymbol{p}} \sim \boldsymbol{p}$. Similarly, the particular form for $\boldsymbol{\phi}$ given by (3.23) is only required when constructing $\boldsymbol{\phi}$ in such a case. This gives rise to the following corollary of Theorem 3.1.6.

Corollary 3.1.8. Given a system of (3.18) and parameter vectors $\boldsymbol{p}, \bar{\boldsymbol{p}} \in \Omega$, suppose that there exists an open neighbourhood $V_{\bar{\boldsymbol{p}}}$ of $\boldsymbol{x}_0(\bar{\boldsymbol{p}})$, and a smooth map $\boldsymbol{\phi} : V_{\bar{p}} \to M(\boldsymbol{p})$ such that [Evans et al., 2005]

$$\boldsymbol{\phi}(\boldsymbol{x}_0(\bar{\boldsymbol{p}})) = \boldsymbol{x}_0(\boldsymbol{p}) \tag{3.27}$$

$$\boldsymbol{f}(\boldsymbol{\phi}(\boldsymbol{x}), \boldsymbol{p}) = \frac{\partial \boldsymbol{\phi}}{\partial \boldsymbol{x}} \boldsymbol{f}(\boldsymbol{x}, \bar{\boldsymbol{p}}) \tag{3.28}$$

$$\boldsymbol{h}(\boldsymbol{\phi}(\boldsymbol{x}), \boldsymbol{p}) = \boldsymbol{h}(\boldsymbol{x}, \bar{\boldsymbol{p}}) \tag{3.29}$$

For all $x \in V_{\bar{\boldsymbol{p}}}$, then $\bar{\boldsymbol{p}} \sim \boldsymbol{p}$.

3.2 Reparameterisation

A reparameterisation procedure may be considered if a system is found to be structurally unidentifiable by using appropriate methods such as the Similarity Transformation approach [Vajda et al., 1989]. The procedure may allow the user to generate a slightly modified version of the original model through reparameterisation of the original system that is at least locally structurally identifiable in the new parameters.

The reparameterisation process may not be entirely appropriate for certain cases and the original model may be a more suitable model. Nevertheless, the reparameterised model may provide additional insight on certain combined parameters, especially if they have any particular physical significance [Evans and Chappell, 2000].

The model (3.1) is considered and it is assumed that the system has been shown to be structurally unidentifiable after analysis by an appropri-

ate method. The reparameterisation methodology using the Taylor Series approach is described in detail in Evans and Chappell [2000] and with the Similarity Transformation approach by Chappell and Gunn [1998].

3.2.1 The Reparameterisation Procedure

Assumption. Theorem 3.1.1 (Similarity Transformation Approach) has been applied to the system (3.1) and that the analytical mapping, $\lambda : V \to \mathbb{R}^n$ of Theorem 3.1.1 has been completely determined as a function of $\boldsymbol{p}$, $\tilde{\boldsymbol{p}}$ and $\tilde{\boldsymbol{x}}$. Suppose that by applying Eqns. (3.15) - (3.17c) it is *not* possible to show that $\tilde{\boldsymbol{p}} = \boldsymbol{p}$. The system is thereby unidentifiable for the experiment considered [Chappell and Gunn, 1998].

Step 1. Suppose that system (3.1) is proven to be structurally unidentifiable, a reparameterised version of the original model (3.1) can be generated. Apply Eqn. (3.17a) - (3.17c) to determine the solution set for the parameter vector $\boldsymbol{p}$. Then expand Eqns. (3.17a) - (3.17c) to yield the following [Chappell and Gunn, 1998]:

$$F_i(\tilde{\boldsymbol{x}}, \boldsymbol{p}, \tilde{\boldsymbol{p}}) = 0, \qquad i = 1, ..., n, \tag{3.30a}$$

$$G_i(\tilde{\boldsymbol{x}}, \boldsymbol{p}, \tilde{\boldsymbol{p}}) = 0, \qquad i = 1, ..., n, \tag{3.30b}$$

$$H_i(\tilde{\boldsymbol{x}}, \boldsymbol{p}, \tilde{\boldsymbol{p}}) = 0, \qquad i = 1, ..., m. \tag{3.30c}$$

where F_i, G_i and H_i are polynomial functions in $\tilde{\boldsymbol{x}}$; with coefficients relying on the vectors $\boldsymbol{p}$ and $\tilde{\boldsymbol{p}}$.

Then, factorise the Taylor Series coefficient of Eqns. (3.30a) - (3.30c), so that the non-zero factors are extracted or eliminated. These non-zero factors are the uniquely identifiable parameters shown in the structural identifiability analysis using the similarity transformation approach. The solution set for the unknown parameter is reduced so is now determined from the following

[Chappell and Gunn, 1998]:

$$\hat{F}_i(\tilde{\boldsymbol{x}}, \boldsymbol{p}, \tilde{\boldsymbol{p}}) = 0, \qquad i = 1, ..., n, \tag{3.31a}$$

$$\hat{G}_i(\tilde{\boldsymbol{x}}, \boldsymbol{p}, \tilde{\boldsymbol{p}}) = 0, \qquad i = 1, ..., n, \tag{3.31b}$$

$$\hat{H}_i(\tilde{\boldsymbol{x}}, \boldsymbol{p}, \tilde{\boldsymbol{p}}) = 0, \qquad i = 1, ..., m, \ . \tag{3.31c}$$

Step 2. Once the Taylor Series expansions of Eqns. (3.30a) - (3.30c) or Eqns. (3.31a) - (3.31c) are determined, apply the jacobian rank test of Pohjanpalo [Pohjanpalo, 1982; Pohjanpalo and Wahlstrom, 1982] with the results of Rothenburg [Rothenburg, 1971]; the (possibly infinite) jacobian matrix of partial derivatives $J(\boldsymbol{p})$ is defined by [Chappell and Gunn, 1998]:

$$J(\boldsymbol{p}) = \begin{bmatrix} \frac{\partial \hat{F}_1^{(0)}}{\partial p_1}(\boldsymbol{p}, \tilde{\boldsymbol{p}}) & \frac{\partial \hat{F}_1^{(0)}}{\partial p_2}(\boldsymbol{p}, \tilde{\boldsymbol{p}}) & \cdots & \frac{\partial \hat{F}_1^{(0)}}{\partial p_p}(\boldsymbol{p}, \tilde{\boldsymbol{p}}) \\ \frac{\partial \hat{F}_1^{(1)}}{\partial p_1}(\boldsymbol{p}, \tilde{\boldsymbol{p}}) & \frac{\partial \hat{F}_1^{(1)}}{\partial p_2}(\boldsymbol{p}, \tilde{\boldsymbol{p}}) & \cdots & \frac{\partial \hat{F}_1^{(1)}}{\partial p_p}(\boldsymbol{p}, \tilde{\boldsymbol{p}}) \\ \vdots & \vdots & & \vdots \\ \frac{\partial \hat{G}_1^{(0)}}{\partial p_1}(\boldsymbol{p}, \tilde{\boldsymbol{p}}) & \frac{\partial \hat{G}_1^{(0)}}{\partial p_2}(\boldsymbol{p}, \tilde{\boldsymbol{p}}) & \cdots & \frac{\partial \hat{G}_1^{(0)}}{\partial p_p}(\boldsymbol{p}, \tilde{\boldsymbol{p}}) \\ \frac{\partial \hat{G}_1^{(1)}}{\partial p_1}(\boldsymbol{p}, \tilde{\boldsymbol{p}}) & \frac{\partial \hat{G}_1^{(1)}}{\partial p_2}(\boldsymbol{p}, \tilde{\boldsymbol{p}}) & \cdots & \frac{\partial \hat{G}_1^{(1)}}{\partial p_p}(\boldsymbol{p}, \tilde{\boldsymbol{p}}) \\ \vdots & \vdots & & \vdots \\ \frac{\partial \hat{H}_1^{(0)}}{\partial p_1}(\boldsymbol{p}, \tilde{\boldsymbol{p}}) & \frac{\partial \hat{H}_1^{(0)}}{\partial p_2}(\boldsymbol{p}, \tilde{\boldsymbol{p}}) & \cdots & \frac{\partial \hat{H}_1^{(0)}}{\partial p_p}(\boldsymbol{p}, \tilde{\boldsymbol{p}}) \\ \frac{\partial \hat{H}_1^{(1)}}{\partial p_1}(\boldsymbol{p}, \tilde{\boldsymbol{p}}) & \frac{\partial \hat{H}_1^{(0)}}{\partial p_2}(\boldsymbol{p}, \tilde{\boldsymbol{p}}) & \cdots & \frac{\partial \hat{H}_1^{(1)}}{\partial p_p}(\boldsymbol{p}, \tilde{\boldsymbol{p}}) \\ \vdots & \vdots & & \vdots \end{bmatrix} \tag{3.32}$$

where $F_i^{(j)}(\boldsymbol{p}, \tilde{\boldsymbol{p}})$, $G_i^{(j)}(\boldsymbol{p}, \tilde{\boldsymbol{p}})$ and $H_i^{(j)}(\boldsymbol{p}, \tilde{\boldsymbol{p}})$, $j = 0, 1, ...$ are the ascending sequences of coefficient functions in the Taylor Series expansions of Eqns. (3.31a)-(3.31c), respectively.

Step 3. Using the generated jacobian matrix, together with and any further information regarding each of the individual parameters, for some $i (1 \leqslant i \leqslant p)$, then apply the following result:

Theorem 3.2.1. For system (3.1) yielding the infinite jacobian matrix Eqn.

(3.32), suppose that rank $J(\boldsymbol{p}) = s$ for some $s < \boldsymbol{p}$ for all $\boldsymbol{p}$ in a neighbourhood of $\boldsymbol{p}_0 \in \Omega$. Then there exist $(p-s)$ redundant parameters for the system (3.1), and, locally, a reparameterisation of system (3.1) in terms of s parameters which is at least locally identifiable for the experiment considered [Chappell and Gunn, 1998; Cobelli and Toffolo, 1987].

Proof of the theorem is shown in Appendix A in Chappell and Gunn [1998].

Step 4. The problem can be reduced to generating a reparameterisation if the rank of Eqn. (3.32) can be (and is) determined; then Theorem 3.2.1 is used to demonstrate the existence of a locally identifiable reparameterised system.

An approach for a system reparameterisation includes grouping the locally identifiable parameters, followed by determining a state space transformation, therefore forming a system that includes only these parameter groupings. The locally identifiable parameter combinations can be established through examination of the null space of an appropriate rank s, $s \times p$ submatrix of the jacobian matrix $J(\boldsymbol{p})$ (Eqn. 3.32).

For instance, if a system has $p = 3$ and $s = 2(= p - 1)$, then the rank deficiency of the jacobian matrix (3.32) is $p - s = 1$. With these conditions, a curve in parameter space will be mapped back from the solution set for the parameters coefficients established from Eqn. (3.31a) - (3.31c) [Chappell and Gunn, 1998].

The nullspace of the jacobian matrix, which is now spanned by $\boldsymbol{n} \in \mathbb{R}^3$, consists of these vector $\boldsymbol{n}$, and satisfy

$$J(\boldsymbol{p}) \cdot \boldsymbol{n} = 0. \tag{3.33}$$

As the nullspace is orthogonal to the parameter axis, the corresponding parameter is said to be locally identifiable if the nullspace includes any zero entries

[Chappell and Gunn, 1998].

For a system with $p = 3$ and $s = 2(= p - 1)$, consider a function of $\boldsymbol{\phi}(p_1, p_2, p_3)$ where $\boldsymbol{\phi} : \Omega \subset \mathbb{R}^3 \to \mathbb{R}$ such that $\boldsymbol{\phi}(\boldsymbol{p})$ is a parameter combination which is locally identifiable. Any $\boldsymbol{\phi}$ will consist of partial derivatives orthogonal to the nullspace, therefore [Chappell and Gunn, 1998]

$$\boldsymbol{n} \cdot \nabla \boldsymbol{\phi} = 0, \tag{3.34}$$

where $\nabla \boldsymbol{\phi}$ represents the gradient of $\boldsymbol{\phi}$ and $\cdot$ represents the standard Euclidean inner product. For instance, when $p = 3$, Eqn. (3.34) is given by [Chappell and Gunn, 1998]

$$\left(n_1 \frac{\partial \boldsymbol{\phi}}{\partial p_1} + n_2 \frac{\partial \boldsymbol{\phi}}{\partial p_2} + n_3 \frac{\partial \boldsymbol{\phi}}{\partial p_3} \right) = 0 \tag{3.35}$$

where $\boldsymbol{\phi}$ is the solution of the partial differential equation [Chappell and Gunn, 1998].

The newly established parameter obtained for $\boldsymbol{\phi}(\boldsymbol{p})$ is said to be locally identifiable, given that the parameter satisfies Eqn. (3.35), nevertheless, there are usually several possible solutions for $\boldsymbol{\phi}(\boldsymbol{p})$ that satisfy Eqn. (3.35) [Chappell and Gunn, 1998].

Therefore, for any nullspace of dimension $p - s$, the concept extends and yields the following [Chappell and Gunn, 1998]:

Theorem 3.2.2. Let $J(\boldsymbol{p})$ be the jacobian matrix defined by Eqn. (3.32) with rank $J(\boldsymbol{p}) = s$ and $\boldsymbol{p} \in \boldsymbol{\Omega}$. Let $N = \{n_1, n_2, ..., n_{p-s}\}$ span the nullspace of $J(\boldsymbol{p})$. Consider any function $\boldsymbol{\phi} : \Omega \subset \mathbb{R}^p \to \mathbb{R}$ which satisfies the orthogonality conditions

$$n_1 \cdot \nabla \boldsymbol{\phi} = 0, \quad i = 1, 2, ..., p - s. \tag{3.36}$$

Then the solution $\boldsymbol{\phi}(\boldsymbol{p})$ of Eqn. (3.36) is a locally identifiable parameter for

the system (3.1) and

$$\boldsymbol{\phi}(p_1, ..., p_p) = (\phi_1, ..., \phi_s) \tag{3.37}$$

is a locally identifiable reparameterisation of Eqn. (3.1) in terms of the s parameters $\{\phi_1, ...\phi_s\}$.

For the proof and further detail of the analysis, see [Chappell and Gunn, 1998].

The reparameterisation of a system of Eqn. (3.1) involves finding the possible solution set of locally identifiable parameter combinations $\boldsymbol{\phi}(\boldsymbol{p})$ which satisfy Eqn. (3.36), then, establishing a parameter space transformation which only involves s of the locally identifiable parameter groupings to re-model the original system equations. However, this transformation process is not required if a noticeable reparameterisation is identified directly from the state equation (3.1). The at least locally identifiable reparameterised system is formed by the new parameter groupings [Chappell and Gunn, 1998].

3.3 Structural Indistinguishability of Models

If a pair of nonlinear models of the same system, but with different mathematical structure, are indistinguishable, then they yield the same response from a particular observation of the system. An indistinguishability analysis is performed by finding and comparing the local, diffeomorphic transformations that relate the model variables for the different pairwise candidates considered [Chapman et al., 1994; Evans et al., 2004]. An indistinguishability analysis can be treated as a generalisation of the identifiability problem, therefore modified versions of strctural identifiability approaches can be applied, e.g. a modified Taylor Series approach [Hattersley et al., 2010].

Consider a pair of models of the same system:

$$\Sigma(\boldsymbol{p}) \begin{cases} \dot{\boldsymbol{x}}(t,\boldsymbol{p}) = \boldsymbol{f}(\boldsymbol{x}(t,\boldsymbol{p}),\boldsymbol{p}) + \boldsymbol{u}(t)\boldsymbol{g}(\boldsymbol{x}(t,\boldsymbol{p}),\boldsymbol{p}) \\ \boldsymbol{y}(t,\boldsymbol{p}) = \boldsymbol{h}(\boldsymbol{x}(t,\boldsymbol{p}),\boldsymbol{p}) \\ \boldsymbol{x}(0,\boldsymbol{p}) = \boldsymbol{x}_0(\boldsymbol{p}) \end{cases} \tag{3.38}$$

$$\tilde{\Sigma}(\tilde{\boldsymbol{p}}) \begin{cases} \dot{\tilde{\boldsymbol{x}}}(t,\tilde{\boldsymbol{p}}) = \tilde{\boldsymbol{f}}(\tilde{\boldsymbol{x}}(t,\boldsymbol{p}),\tilde{\boldsymbol{p}}) + \boldsymbol{u}(t)\tilde{\boldsymbol{g}}(\tilde{\boldsymbol{x}}(t,\tilde{\boldsymbol{p}}),\tilde{\boldsymbol{p}}) \\ \tilde{\boldsymbol{y}}(t,\tilde{\boldsymbol{p}}) = \tilde{\boldsymbol{h}}(\tilde{\boldsymbol{x}}(t,\tilde{\boldsymbol{p}}),\tilde{\boldsymbol{p}}) \\ \tilde{\boldsymbol{x}}(0,\tilde{\boldsymbol{p}}) = \tilde{\boldsymbol{x}}_0(\tilde{\boldsymbol{p}}) \end{cases} \tag{3.39}$$

where $\boldsymbol{x}(t,\boldsymbol{p}) \in \mathbb{R}^n$ and $\tilde{\boldsymbol{x}}(t,\tilde{\boldsymbol{p}}) \in \mathbb{R}^n$ denote the state variables and $\boldsymbol{y}(t,\boldsymbol{p}) \in \mathbb{R}^m$ and $\tilde{\boldsymbol{y}}(t,\tilde{\boldsymbol{p}}) \in \mathbb{R}^m$ denote the state outputs. The functions $\boldsymbol{f}$, $\tilde{\boldsymbol{f}}$, $\boldsymbol{g}$, $\tilde{\boldsymbol{g}}$, $\boldsymbol{h}$ and $\tilde{\boldsymbol{h}}$ are assumed to be analytic. Both models (3.38) and (3.39) have the same number of output variables.

By definition, the systems $\Sigma(\boldsymbol{p})$ and $\tilde{\Sigma}(\tilde{\boldsymbol{p}})$, given that $\boldsymbol{p} \in \Omega$ and $\tilde{\boldsymbol{p}} \in \tilde{\Omega}$, are said to be output indistinguishable (denoted by $\Sigma(\boldsymbol{p}) \sim \tilde{\Sigma}(\tilde{\boldsymbol{p}})$), if $\boldsymbol{y}(t,\boldsymbol{p}) = \tilde{\boldsymbol{y}}(t,\tilde{\boldsymbol{p}})$ for all t. Similarly $\Sigma(\boldsymbol{p})$ and $\tilde{\Sigma}(\tilde{\boldsymbol{p}})$ are structurally indistinguishable if, for generic $\boldsymbol{p} \in \Omega$ there exists a $\tilde{\boldsymbol{p}} \in \Omega$ s.t. $\Sigma(\boldsymbol{p}) \sim \tilde{\Sigma}(\tilde{\boldsymbol{p}})$.

Approaches exist for determining the structural indistinguishability of candidate nonlinear models and these are based upon the Similarity Transformation approach also used for identifiability analysis [Chapman et al., 1994; Evans et al., 2004]. However, since the analysis is fundamentally based upon comparison of the observations, an approach using Taylor Series expansions [Pohjanpalo, 1978; Hattersley et al., 2010] of the relative system observations can also be applied.

3.4 Parameter Estimation

Parameter estimation is an *a posteriori* procedure. Besides the uniqueness of the parameters or system, the *a priori* analysis does not provide information such as actual parameter values. Therefore, a structurally identifiable model is usually tested with an *a posteriori* analysis after a satisfying an *a priori* test. Usually, the model is fitted to a set (or sets) of observation data to obtain a set of estimated values for the system parameters. Nevertheless, a set of observed data is not perfect or noise free, i.e. it is a set of observation with experimental/measurement/system or noise errors. Therefore, a structurally globally identifiable model does not guarantee good parameter estimation [Jacquez, 1999].

Many software packages available allow their users to estimate the model's unknown parameters. These packages are generally numerically robust and are widely used by modellers to perform parameter fitting, especially those with complex mathematical structures. However, many software packages also fit the model to any data unconditionally, therefore giving a false impression that the model is numerically identifiable; these problems can be overcome by judging the quality of the parameters estimated by the variances and covariances (or covariance matrix), and these are usually also provided in many packages. [Jacquez, 1999].

In this thesis, FACSIMILE (MCPA Software, UK) is used for the parameter estimation. FACSIMILE is a robust modelling computer package designed to solve differential equations of the kinetics of physical and chemical system models. It contains a different variety of differential equation solvers and can handle very stiff systems with its robust numerical integrator [AEA Technology, 1995]. For parameter fitting, it uses a Newton iterative method which provides a predictor-corrector technique applied to the differential equations

and is able to solve differential equations simultaneously [AEA Technology, 1995; Cheung et al., 2008].

FACSIMILE consists of a feature that allows its users to statistically study the quality of the parameter values fitted to the data and model, i.e. the goodness of fit. This feature includes information such as the Residual Sum of Squares (RSS), whereby

$$RSS = \sum_{i=1}^{r} \sum_{j=1}^{n} \left(\frac{y_{obs,i}(j) - y_{sim,i}(t_j)}{\sigma_i} \right)^2 \tag{3.40}$$

where $y_{sim,i}(t_j)$ represents the ith output of the model at the jth sampling time (t_j); $y_{obs,i}(j)$ denotes the corresponding experimental data point; and σ_i denotes the estimation of the standard error for the ith output and R_i represents the range for $y_{sim,i}(t_j)$ [AEA Technology, 1995; Cheung et al., 2008].

The statistical analysis within FACSIMILE also provides the confidence levels of the parameters fitted to the model and data which allow users to study how well the parameters are determined. However, if a parameter is not well-determined, it will not be defined within the required 'confidence levels'. The statistics show the standard deviation of the natural logarithm (SDLN) of all of the well-determined parameters, which is obtained from the variance-covariance matrix and the estimated correlation between well-determined parameters [AEA Technology, 1995; Cheung et al., 2008].

3.4.1 Data

In this thesis two types of experimental data are considered, the intravenous glucose tolerance test (IVGTT) and glycemic clamp data. All data used within this thesis were provided by Professor Leon Aarons, School of Pharmacy and Pharmaceutical Sciences, Manchester University [Mills, 2007]. Data sets include IVGTT and glycemic clamp data collected from 28 subjects.

Subject	Duration (min)	NODP	Subject	Duration (min)	NODP
1	241	16	15	241	16
2	241	16	16	41	11
3	241	15	17	81	12
4	241	16	18	81	13
5	240	15	19	241	14
6	121	14	20	60	11
7	241	16	21	239	15
8	120	13	22	240	15
9	121	12	23	180	13
10	241	15	24	241	15
11	181	14	25	80	12
12	181	13	26	121	13
13	121	13	27	241	15
14	246	15	28	110	13

NODP represents number of data point

Table 3.1: IVGTT data sets of all subjects.

For the IVGTT data, the subjects were given a single injection of a dose of 300mg glucose follow by frequent blood sampling to measure the glucose and insulin concentrations in blood. These data sets include IVGTTs that lasted approximately, 40, 60, 80, 120, 180 and 240 minutes where the majority of IVGTTs lasted 240 minutes (See Table 3.1). For a typical IVGTT, The blood samplings usually began straight after the glucose injection at intervals of 1-2 minutes for the first 7 minutes, followed by intervals of 5 - 10 minutes for approximately 50 minutes and then at 1, 1.5, 2, 3, and 4 hours [Mills, 2007]. Figure 3.1 shows the typical glucose-insulin response of a 240 minute-long IVGTT and the data set is given in Table 3.2 (See Appendix C for more IVGTT data sets).

For a glycemic clamp, an initial blood sample is usually measured to determine the basal levels of glucose and insulin concentration. Glucose concentration for these subjects is raised to a target level and is maintained at this level with adapted glucose infusion for 8 hours. The glucose and insulin concentration levels are monitored every 10 to 30 minutes. Figure 3.2 shows

the typical glucose-insulin response during a glycemic clamp and Table 3.3 shows the data set for the clamp [Mills, 2007].

Time (min)	Glucose (mmol/L)	Insulin (mU/L)
0	5.1	9.0
1	5.5	9.0
3	19.3	81.9
5	17.9	127.6
7	16.1	101.9
12	14.2	63.8
16	13.4	60.1
21	12.6	47.2
26	11.6	39.1
31	10.6	32.6
41	9.5	32.4
61	7.6	25.3
81	6.2	17.7
121	4.8	7.7
181	4.7	6.8
241	5.1	8.3

Table 3.2: A typical set of IVGTT data with a duration of approximately 240 minutes.

3.5 Conclusion

In this thesis, structural identifiability analysis will be performed on various glucose-insulin dynamic models including different forms of the well-referenced Minimal Model. Although some of these models have been around for many years, unfortunately no structural identifiability analyses has seemingly been performed/published on these particular forms of the models. Since some of these models are well-referenced, and used in the medical setting, it is important that the structural identifiability of these glucose-insulin dynamics models is established. For the structural identifiability analyses, glucose and insulin are assumed observable and measurable through blood sampling. Therefore, the system observation is given by

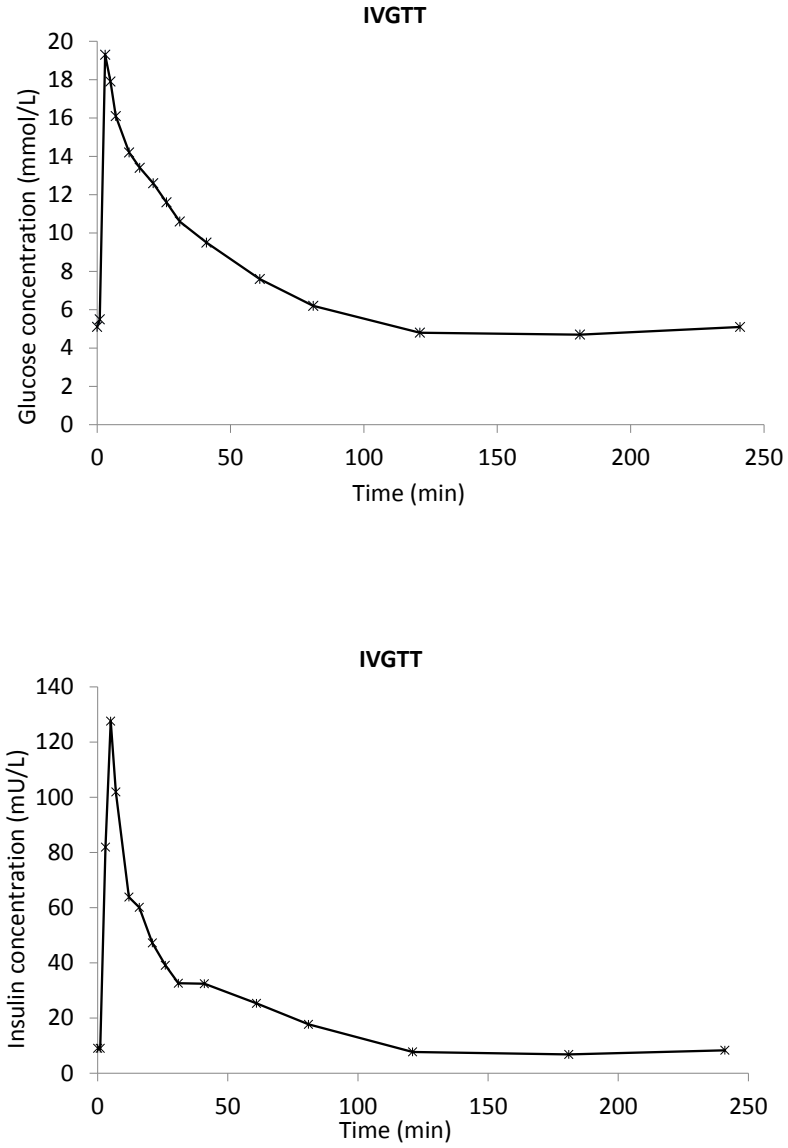

Figure 3.1: Example of glucose-insulin dynamics during an IVGTT.

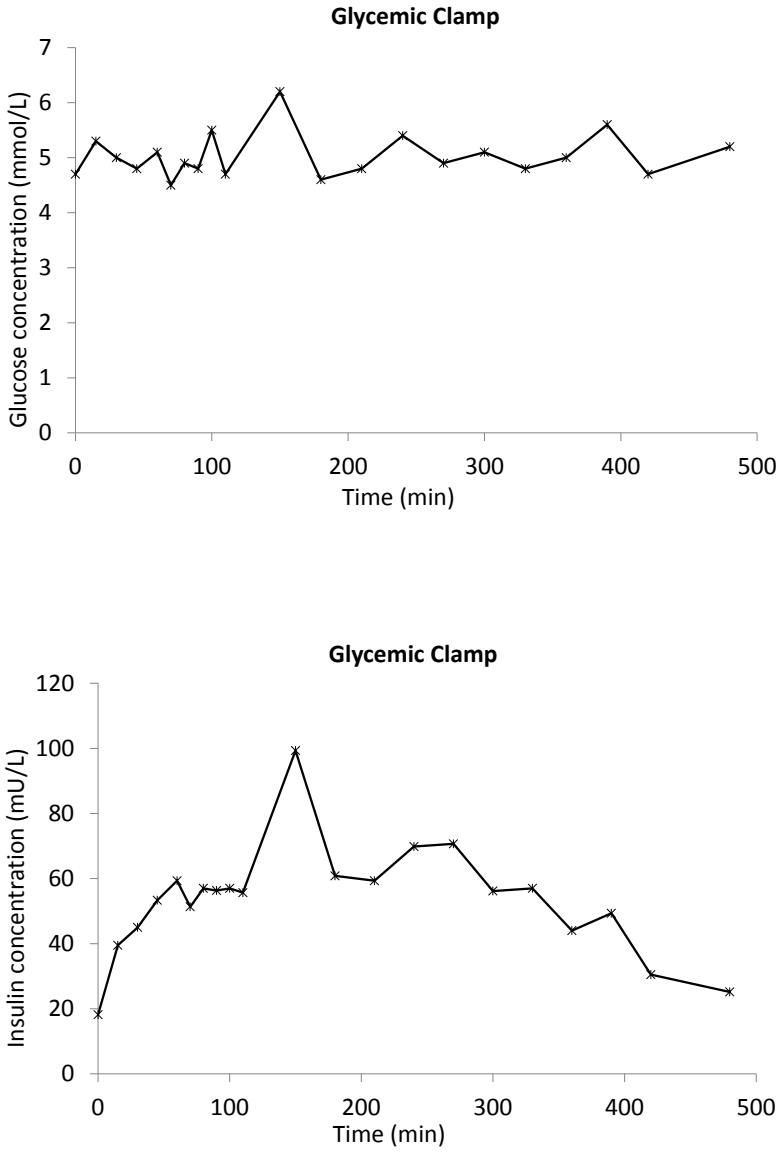

Figure 3.2: Example of glucose and insulin dynamics during a glycemic clamp experiment.

Time (min)	Glucose (mmol/L)	Insulin (mU/L)	Time (min)	Glucose (mmol/L)	Insulin (mU/L)
0	4.7	18.17	180	4.6	59.33
15	5.3	39.50	210	4.8	59.33
30	5.0	45.00	240	5.4	69.83
45	4.8	53.55	270	4.9	70.67
60	5.1	59.33	300	5.1	56.17
70	4.5	51.33	330	4.8	57.00
80	4.9	57.00	370	5.0	44.00
90	4.8	56.33	390	5.6	49.33
100	5.5	57.00	420	4.7	30.50
110	4.7	55.67	480	5.2	25.17
150	6.2	99.33			

Table 3.3: An example of a set of glycemic clamp data.

$$\boldsymbol{y}(t) = \begin{bmatrix} y_1(t) \\ y_2(t) \end{bmatrix} = \begin{bmatrix} G(t) \\ I(t) \end{bmatrix} \tag{3.41}$$

where $G(t)$ represents glucose concentration and $I(t)$ represents insulin concentration. All of the analyses are performed under the assumption of a perfect, noise-free environment. The structural identifiability analyses are performed on glucose-insulin dynamics using the Taylor Series approach (See Section 3.1.2), the Similarity Transformation approach (See Section 3.1.3) and its forms (See Section 3.1.4) for autonomous nonlinear systems.

This thesis demonstrates that more than one approach is required for the structural identifiability of some glucose-insulin models due to the complexity of the structure of the models. However, if the structural identifiability for a glucose-insulin model is proven to be challenging, i.e. without conclusive results using various approaches, a simple and direct approach can be used to determine whether the model is actually unidentifiable (see Section 3.1.5). However, this approach does not provide sufficient information regarding to the structure of the unknown parameters within the system.

One of the glucose-insulin models proves to be structural unidentifiable.

Therefore, a reparameterisation is performed on this model to yield an, at least, locally identifiable model using the process and Theorem given in Section 3.2.

A structural indistinguishability analysis (See Section 3.3) is applied to compare the CLMM to the EMM, to determine if these models with different model structure are distinguishable for standard observations available or experiments performed.

Chapter 4

Structural Identifiability of The Minimal Model

4.1 Structural Identifiability Analysis

The Original Minimal Model (OMM) and Extended Minimal Model (EMM) are the most widely used versions of the Minimal Model (MM), and also can conceivably be considered as the most widely used of all glucose-insulin dynamics models. However, despite their universal application, as far as this author is aware, structural identifiability analysis for these two specific forms of the MM has never been published.

The structural identifiability analysis of a modified version of OMM, the New Minimal Model (NMM) shows that the NMM is structurally identifiable with known conditions. However, the structural uniqueness of the NMM does not infer that the OMM and EMM are also globally structurally identifiable, since these three models have different mathematical structures.

The two forms of MM that are analysed in this thesis are the OMM

and EMM. The system equations for the OMM are given by

$$\dot{G}(t) = -\big[p_1 + X(t)\big]G(t) + p_1 G_b, \qquad G(0) = G_0 \tag{4.1}$$

$$\dot{X}(t) = -p_2 X(t) + p_3[I(t) - I_b], \qquad I(0) = I_0 = p_7 + I_b \tag{4.2}$$

and the system equations for the EMM are given by

$$\dot{G}(t) = -[p_1 + X(t)]G(t) + p_1 G_b \qquad G(0) = G_0 \tag{4.3}$$

$$\dot{X}(t) = -p_2 X(t) + p_3[I(t) - I_b] \qquad X(0) = 0 \tag{4.4}$$

$$\dot{I}(t) = p_4 t[G(t) - p_5] - p_6[I(t) - I_b], \; G(t) > p_5, \qquad I(0) = p_7 + I_b \tag{4.5a}$$

$$\dot{I}(t) = -p_6[I(t) - I_b] \qquad G(t) < p_5 \tag{4.5b}$$

where $G(t)$ represents the glucose concentration at time t, $I(t)$ the insulin concentration at time t and $X(t)$ the insulin action at time t. Parameters G_b and I_b are the basal levels of glucose and insulin concentration respectively (See Chapter 2 , Section 2.4).

To truly analyse the structural identifiability of the EMM and OMM, several different analyses have been carried out incorporating the use of a symbolic computational tool, Mathematica [Wolfram, 1996]. For robust parameter estimation it is important to establish the uniqueness or otherwise of the unknown model parameters when both the OMM, and the EMM are used at both of the pre- and post-switching phases, where the pre-switching phase is represented by Eqns. (4.3), (4.4) and (4.5a) and the post-switching phase by Eqns. (4.3), (4.4) and (4.5b). We assume that the observations of the system are both glucose and insulin concentrations. The observations of the model

are therefore given by

$$y_1(t) = G(t)$$
$$y_2(t) = I(t).$$

4.2 Structural Identifiability of the OMM

The OMM is considered as one of the most known forms of the MM as it is widely used to determine insulin sensitivity index of different individuals or subject or animal groups through oral and intravenous glucose tolerance tests. Therefore, it is essential to determine whether this particular form of the MM is indeed *a priori* identifiable.

For the OMM , the Taylor Series approach of Pohjanpalo is used [Pohjanpalo, 1978]. The system equations of the OMM are given by

$$\dot{G}(t) = -[p_1 + X(t)]G(t) + p_1 G_b$$
$$\dot{X}(t) = -p_2 X(t) + p_3[I(t) - I_b]$$

with observations

$$y_1(t) = G(t) \tag{4.6}$$
$$y_2(t) = I(t) \tag{4.7}$$

and the initial conditions are given by

$$G(0) = G_0$$
$$X(0) = 0$$
$$I(0) = I_0.$$

The vector of unknown parameters is given by

$$\boldsymbol{p} = [p_1, p_2, p_3, G_b, I_b].$$

The first coefficient of the Taylor Series expansion for $y_1(t)$ gives

$$y_1(t) = G(t)$$

thus

$$y_1(0) = G_0$$

Thus G_0 is uniquely identifiable.

The second coefficient of the Taylor Series expansion, evaluated at $t = 0$ gives

$$\dot{y_1}(t) = -[p_1 + X(t)]G(t) + p_1 G_b$$

thus

$$\dot{y_1}(0) = -p_1 G_0 + p_1 G_b$$

whereby

$$p_1 = \frac{\dot{y_1}(0)}{(-G_0 + G_b)} \ . \tag{4.8}$$

This implies that the parameter p_1 is uniquely identifiable if G_b is known. Since G_b, the glucose basal level is usually measurable, we can assume that G_b is known and therefore the parameter p_1 is uniquely identifiable.

The third coefficient of the Taylor Series expansion and evaluation at $t = 0$ give

$$\ddot{y_1}(0) = -p_1[-p_1 G_0 + p_1 G_b] - p_3 G_0[I_0 - I_b]$$

whereby

$$p_3 = \frac{-\ddot{y_1}(0) - p_1[-p_1 G_0 + p_1 G_b]}{G_0[I_0 - I_b]} \tag{4.9}$$

and after substituting for parameter p_1 from (4.8) this gives

$$p_3 = \frac{\dot{y}_1^2(0) - G_0\ddot{y}_1(0) + G_b\ddot{y}_1(0)}{G_0(G_0 - G_b)(I_0 - I_b)}. \tag{4.10}$$

This implies that the parameter p_3 is identifiable if G_b and I_b are known. Since the basal level for insulin I_b is normally measurable (therefore known) at steady state, therefore the parameter p_3 is also uniquely identifiable.
The fourth coefficient of the Taylor Series expansion at $t = 0$ is given by

$$\dddot{y}_1(0) = -p_1\ddot{y}_1(0) - 2\dot{y}_1(0)p_3[I_0 - I_b] - G_0(-p_2p_3(I_0 - I_b) + p_3\dot{I}(0)).$$

whereby

$$p_2 = \frac{-\dddot{y}_1(0) - p_1\ddot{y}_1(0) - 2\dot{y}_1(0)p_3[I_0 - I_b]}{G_0p_3(I_0 - I_b)} - \frac{\dot{I}(0)}{I_0 - I_b}$$

and substituting for p_1 from (4.8) and p_3 from (4.10) gives

$$\begin{aligned} p_2 = {} & \frac{1}{(G_0(I_0 - I_b)(-\dot{y}_1^2(0) + (G_0 - G_b)\ddot{y}_1(0)} \\ & \times \Big(I_b(2\dot{y}_1^3(0) + \dot{y}_1(0)(-3G_0\ddot{y}_1(0) + 2G_b\ddot{y}_1(0)) \\ & + G_0(G_0 - G_b)\dddot{y}_1(0)) + I_0(-2\dot{y}_1^3(0) + (3G_0 - 2G_b)\dot{y}_1(0)\ddot{y}_1(0) \\ & + G_0(-G_0 + G_b)\dddot{y}_1(0) + G_0(-\dot{y}_1^2(0) + (G_0 - G_b)\ddot{y}_1)\dot{I}(0)\Big). \end{aligned} \tag{4.11}$$

This implies that parameter the p_2 can only be determined if $\dot{I}(0)$ is known.

This analysis shows that only parameters p_1 and p_3 are uniquely identifiable under the condition that the basal levels of glucose and insulin are known. It is evident from this expression that, without further information regarding the insulin time course via incorporation of Eqn. (4.5a) or (4.5b), the parameter p_2 cannot be uniquely identified, nor from higher order Taylor Series coefficients due to the fact that higher derivatives of the insulin variable

also enter into these coefficients. Thus not all of the model parameters can be uniquely identified for the OMM, Eqns. (4.1) and (4.2) for observation of glucose alone using this approach.

This could lead to problems at the *a posteriori*, numerical identifiability stage when parameter estimations are sought. For example, Pillonetto et al [Pillonetto et al., 2003] have commented that the parameters p_2 and p_3 are at risk of being numerically non-identifiable. This could lead to a major problem, as the unidentifiable parameter p_2 is one of the key parameters required in order to determine the insulin sensitivity index,

$$S_I = \frac{p_3}{p_2}.$$

4.3 Structural Identifiability of the EMM Over the Post-Switching Phase

The post-switching phase of the EMM describes the decay of the insulin concentration in blood after the glucose level has lowered below the threshold level p_5. For the post-switching state (when $G(t) < p_5$), the Taylor Series approach of Pohjanpalo is used for the structural identifiability analysis [Pohjanpalo, 1978] with the following system equations

$$\begin{aligned}
\dot{G}(t) &= -[p_1 + X(t)]G(t) + p_1 G_b \\
\dot{X}(t) &= -p_2 X(t) + p_3[I(t) - I_b] \\
\dot{I}(t) &= -p_6[I(t) - I_b].
\end{aligned}$$

The initial conditions are given by

$$G(0) = G_0$$
$$X(0) = 0$$
$$I(0) = I_0 = I_b + p_7$$

with observations

$$y_1(t) = G(t) \tag{4.12}$$
$$y_2(t) = I(t). \tag{4.13}$$

The vector of unknown parameters for the EMM at the post-switching phase is given by

$$\boldsymbol{p} = [p_1, p_2, p_3, p_6, p_7, G_b, I_b, G_0].$$

The first coefficients of the Taylor Series expansions and their evaluations at $t = 0$ are given by

$$y_1(t) = G(t)$$
$$y_1(0) = G_0 \tag{4.14}$$
$$y_2(t) = I(t)$$
$$y_2(0) = I_0. \tag{4.15}$$

Thus G_0 and I_0 are uniquely identifiable.

The second coefficients of the Taylor Series expansion and their evaluations at

$t = 0$ are given by

$$\dot{y}_1(t) = -[p_1 + X(t)]G(t) + p_1 G_b$$
$$\dot{y}_1(0) = -p_1 G_0 + p_1 G_b$$
$$\dot{y}_2(t) = -p_6[I(t) - I_b]$$
$$\dot{y}_2(0) = -p_6[I_0 - I_b]$$

whereby

$$p_1 = \frac{\dot{y}_1(0)}{G_b - y_1(0)} \tag{4.16}$$

and

$$p_6 = \frac{\dot{y}_2(0)}{I_b - y_2(0)}. \tag{4.17}$$

These imply that the parameter p_1 is uniquely identifiable if G_b is known; and p_6 is uniquely identifiable if I_b is known.

The third coefficient of the Taylor Series expansions and their evaluations at $t = 0$ are given by

$$\ddot{y}_1(t) = -y_1(t)(-p_2 X(t) + p_3(-I_b + y_2(t))) + (-p_1 - X(t))\dot{y}_1(t)$$
$$\ddot{y}_1(0) = -p_1\dot{y}_1(0) - p_3 y_1(0)(y_2(0) - I_b)$$
$$\ddot{y}_2(t) = p_6^2(y_2(t) - I_b)$$
$$\ddot{y}_2(0) = p_6^2(y_2(0) - I_b)$$

whereby

$$p_3 = \frac{-\dot{y}_1^2(0) - \ddot{y}_1(0)G_b + \ddot{y}_1(0)y_1(0)}{y_1(0)(-G_b + y_1(0))(I_b - y_2(0))} \tag{4.18}$$

and

$$I_b = \frac{-\dot{y}_2^2(0) + \ddot{y}_2(0)y_2(0)}{\ddot{y}_2(0)}. \tag{4.19}$$

These imply that the parameter I_b is uniquely identifiable and the parameter

p_3 is uniquely identifiable if G_b is known. Therefore, the parameters p_6 and p_7 are also uniquely identifiable from (4.15) and (4.17) respectively.

The fourth coefficients of the Taylor Series expansions and their evaluations at $t = 0$ (noting that the additional derivatives of y_2 yield no further information) are given by:

$$\begin{aligned}
\dddot{y}_1(t) =& 2\dot{y}_1(t)(p_3 I_b + p_2 X(t) - p_3 y_2(t)) \\
& - y_1(t)(p_2^2 X(t) + p_3(p_2 I_b - p_2 y_2(t) + \dot{y}_2(t))) - \ddot{y}_1(t)(-p_1 + X(t)) \\
\dddot{y}_1(0) =& 2p_3(I_b - y_2(0))\dot{y}_1(0) - p_3 y_1(0)(p_2(I_b - \dot{y}_2(0)) - p_1 \ddot{y}_1(0)
\end{aligned}$$

whereby

$$\begin{aligned}
p_2 =& \frac{2\dot{y}_1^3(0)\dot{y}_2(0) + \ddot{y}_1(0)\dot{y}_1(0)\dot{y}_2(0)(2G_b - 3y_1(0)) + \ddot{y}_2(0)y_1(0)}{\dot{y}_2(0)(\dot{y}_1^2(0) + \ddot{y}_1(0)(G_b - y_1(0)))y_1(0)} \\
& + \frac{(\ddot{y}_1(0)\ddot{y}_2(0) - \dddot{y}_1(0)\dot{y}_2(0))(G_b - y_1(0)) + y_1(0)}{\dot{y}_2(0)(\dot{y}_1^2(0) + \ddot{y}_1(0)(G_b - y_1(0)))y_1(0)}.
\end{aligned} \tag{4.20}$$

This implies that the parameter p_2 is uniquely identifiable if G_b is known. The fifth coefficients of the Taylor Series expansions and their evaluations at $t = 0$ are given by

$$\begin{aligned}
y_1^{(4)}(t) =& -3\dot{y}_1(t)(p_2^2 X(t) + p_3(p_2 I_b - p_2 y_2(t) + \dot{y}_2(t))) \\
& + 3\ddot{y}_1(t)(p_2 X(t) + p_3(I_b - y_2(t))) \\
& + y_1(t)(p_2^3 X(t) + p_3(p_2^2 I_b - p_2^2 y_2(t) + p_2 \dot{y}_2(t) - \ddot{y}_2(t))) \\
& - \dddot{y}_1(t)(p_1 + X(t)) \\
y_1^{(4)}(0) =& -3p_3\dot{y}_1(0)(p_2(I_b - y_2(0)) + \dot{y}_2(0)) + 3p_3\ddot{y}_1(0)(I_b - y_2(0)) \\
& + p_3 y_1(0)(p_2^2(I_b - y_2(0)) + p_2\dot{y}_2(0) - \ddot{y}_2(0)) - p_1\dddot{y}_1(0),
\end{aligned}$$

whereby,

$$
\begin{aligned}
G_b = \pm\Big(& -4\dot{y}_1^4(0)\dot{y}_2^2(0)\ddot{y}_1(0) + G_0\dot{y}_1^3(0)\dot{y}_2(0)(4\ddot{y}_1(0)\ddot{y}_2(0) - \dot{y}_2(0)\dddot{y}_1(0)) \\
& -G_0\dot{y}_1^2(0)(-2G_0\ddot{y}_1(0)\ddot{y}_2^2(0) + G_0\dot{y}_2(0)\ddot{y}_2(0)\dddot{y}_1(0) + \dot{y}_2^2(0)(-9\ddot{y}_1^2(0) \\
& +G_0 y_1^{(4)}(0))) + 2G_0^2(-G_0\ddot{y}_1^2(0)\ddot{y}_2^2(0) + G_0\dot{y}_2(0)\ddot{y}_1(0)\ddot{y}_2(0)\dddot{y}_1(0) \\
& + \dot{y}_2^2(0)(-3\ddot{y}_1^3(0) - G_0\dddot{y}_1^2(0) + G_0\ddot{y}_1(0)y_1^{(4)})) + G_0\dot{y}_1(0)\dot{y}_2(0)(G_0\ddot{y}_1(0) \\
& \times(-5\ddot{y}_1(0)\ddot{y}_2(0) + 3\dot{y}_2(0)y_1^{(3)}(0)) + \sqrt{\Big(}9\dot{y}_1^4(0)\dot{y}_2^2(0)\dddot{y}_1^2(0) \\
& -2\dot{y}_1^3(0)\dot{y}_2(0)\dddot{y}_1(0)(3G_0\ddot{y}_2(0)\dddot{y}_1(0) + \dot{y}_2(0)(9\ddot{y}_1^2(0) - G_0 y_1^{(4)}(0))) \\
& -2G_0\dot{y}_1(0)(-3G_0\ddot{y}_1^2(0)\dddot{y}_1(0) + \dot{y}_2(0)\ddot{y}_1(0)\ddot{y}_2(0)(3\ddot{y}_1^3(0) + G_0\dddot{y}_1^2(0) \\
& +G_0\ddot{y}_1(0)y_1^{(4)}(0)) + \dot{y}_2^2(0)\dddot{y}_1(0)(-13\ddot{y}_1^3(0) - 2G_0\dddot{y}_1^2(0) \\
& + 3G_0\ddot{y}_1(0)y_1^{(4)}(0))) + G_0\ddot{y}_1^2(0)(-3G_0\ddot{y}_1^2(0) + 2G_0\dot{y}_2(0)\ddot{y}_1(0)\ddot{y}_2(0)\dddot{y}_1(0) \\
& + \dot{y}_2^2(0)(-12\ddot{y}_1^3(0) - 3G_0\dddot{y}_1^2(0) + 4G_0\ddot{y}_1(0)y_1^{(4)})) + \dot{y}_1^2(0)(-3G_0^2\ddot{y}_2^2(0)\ddot{y}_1^2(0) \\
& +2G_0\dot{y}_2(0)\ddot{y}_2(0)\dddot{y}_1(0)(6\ddot{y}_1^2(0) + G_0 y_1^{(4)}(0)) + \dot{y}_2^2(0)(9\ddot{y}^2(0) \\
& -14G_0\ddot{y}_1(0)\dddot{y}_1^2(0) - 2G_0\ddot{y}_1^2(0)y_1^{(4)}(0) + G_0^2(y_1^{(4)}(0))^2))))\Big)\Big/ \\
& \Big(2(2\dot{y}_1^2(0)\dot{y}_2^2(0)\ddot{y}_1^2(0) + G_0\dot{y}_1(0)\dot{y}_2(0)\ddot{y}_1(0)(-2\ddot{y}_1(0)\ddot{y}_2(0) + \dot{y}_2(0)\dddot{y}_1(0)) \\
& +G_0(-G_0\ddot{y}_1^2(0)\ddot{y}_2^2(0) + G_0\dot{y}_2(0)\ddot{y}_1(0)\ddot{y}_2(0)\dddot{y}_1(0) + \dot{y}_2^2(0)(-3\ddot{y}_1^3(0) \\
& -G_0\dddot{y}_1^2(0) + G_0\ddot{y}_1(0)y_1^{(4)}(0)))\Big).
\end{aligned}
$$

This implies that there are at least two solutions for the parameter G_b, and the parameter may not be uniquely identifiable (if not previously known). Calculation of higher order coefficients does not permit further inference on the solutions for this parameter. The result shows that the parameters p_1, p_2,

p_3, p_6, p_7 and I_b are uniquely identifiable only if the parameter G_b is known or measurable. This shows that the model is structurally globally identifiable given that the basal level of glucose (G_b) is known.

The structural identifiability analysis for the EMM at the post-switching phase can only provide information on a subset of the unknown parameters since p_4 and p_5 are not present in the differential equations for insulin, due to the elimination of the time term at the post-switching phase. However, the analysis over the post-switching phase can still be used in conjunction with the results obtained over the pre-switching phase. Due to the large number of coefficients generated by the Taylor Series expansion, part of the analysis was performed with the aid of Mathematica [Wolfram, 1996], a symbolic computational software tool.

4.4 Structural Identifiability of the EMM Over the Pre-Switching Phase

A structural identifiability analysis of the EMM over the pre-switching phase when $G(t) > p_5$ was also performed using the Taylor Series approach. The system equations for the EMM over the pre-switching phase are given by:

$$\begin{aligned}
\dot{G}(t) &= -[p_1 + X(t)]G(t) + p_1 G_b \\
\dot{X}(t) &= -p_2 X(t) + p_3[I(t) - I_b] \\
\dot{I}(t) &= p_4 t[G(t) - p_5] - p_6[I(t) - I_b].
\end{aligned}$$

with observations

$$y_1(t) = G(t) \tag{4.21}$$

$$y_2(t) = I(t). \tag{4.22}$$

The initial conditions here are given by

$$G(0) = G_0$$

$$X(0) = 0$$

$$I(0) = I_0 = I_b + p_7.$$

The vector of unknown parameters for EMM at pre-switching phase is given by

$$\boldsymbol{p} = [p_1, p_2, p_3, p_4, p_5, p_6, p_7, I_b, G_b].$$

The first coefficients of the Taylor Series expansions and their evaluations at $t = 0$ are given by

$$y_1(t) = G(t)$$

$$y_1(0) = G_0 \tag{4.23}$$

$$y_2(t) = I(t)$$

$$y_2(0) = I_0. \tag{4.24}$$

Thus G_0 and I_0 are uniquely identifiable as before.

The second coefficients of the Taylor Series expansions and their evaluations

at $t = 0$ are given by

$$\begin{aligned}
\dot{y}_1(t) &= -(p_1 + X(t))G(t) + p_1 G_b \\
\dot{y}_1(0) &= -p_1 G_0 + p_1 G_b \\
\dot{y}_2(t) &= -p_6(I(t) - I_b) \\
\dot{y}_2(0) &= -p_6(I_0 - I_b)
\end{aligned}$$

whereby

$$p_1 = \frac{\dot{y}_1(0)}{G_b - y_1(0)} \tag{4.25}$$

and

$$p_6 = \frac{\dot{y}_2(0)}{I_b - y_2(0)}. \tag{4.26}$$

Thus Eqn. (4.25) implies that parameter p_1 is uniquely identifiable if G_b is known and Eqn. (4.26) implies that parameter p_6 is uniquely identifiable if I_b is also known.

The third coefficients of the Taylor Series expansions and their evaluations at $t = 0$ are given by

$$\begin{aligned}
\ddot{y}_1(t) =& (G_b p_1 + G(t)(-p_1 - X(t)))(-p_1 - X(t)) \\
&- G(t)(p_3(-I_b + I(t)) - p_2 X(t)) \\
\ddot{y}_1(0) =& - p_1(-G_0 p_1 + G_b p_1) - G_0 p_3(I_0 - I_b) \\
\ddot{y}_2(t) =& - p_4 p_5 - p_6^2 I_b + p_6^2 I(t) + G_b p_1 p_4 t + p_4 p_5 p_6 t \\
&- p_4 G(t)(-1 + t(p_1 + p_6 + X(t))) \\
\ddot{y}_2(0) =& p_4(G_0 - p_5) + p_6^2(I_0 - I_b)
\end{aligned}$$

whereby

$$p_3 = \frac{\dot{y}_1^2(0) + \ddot{y}_1(0)(G_b - y_1(0))}{(G_b - y_1(0))(I_b - y_2(0))y_1(0)} \tag{4.27}$$

and

$$p_4 = -\frac{\dot{y}_2^2(0) + \ddot{y}_2(0)(I_b - y_2(0))}{(p_5 - y_1(0))(I_b - y_2(0))}. \tag{4.28}$$

Thus Eqn. (4.27) implies that the parameter p_3 is uniquely identifiable if G_b and I_b are known and Eqn. (4.28) implies that the parameter p_4 is uniquely identifiable if the parameters p_5 and I_b are known.

The fourth coefficients of the Taylor Series expansions and their evaluations at $t = 0$ are given by

$$\begin{aligned}\dddot{y}_1(0) =& G_b p_1(p_1^2 + 2p_3(-I_0 + I_b)) - G_0(p_1^3 - p_3(p_2 + p_6)(I_0 - I_b) \\ &+ 3p_1p_3(-I_0 + I_b))\end{aligned}$$

$$\dddot{y}_2(0) = 2(-G_0p_1 + G_bp_1)p_4 - p_6(p_4(G_0 - p_5) + p_6^2(I_0 - I_b))$$

whereby

$$\begin{aligned}p_2 =& \frac{-\dot{y}_1^2(0)\dot{y}_2(0)G_0 - G_0\ddot{y}_1(0)\dot{y}_2(0)(G_b - G_0)}{\dot{y}_1^2(0) + \dot{y}_1(0)(G_b - G_0)G_0(I_b - I_0)} \\ &+ \frac{\dddot{y}_1(0)(I_b - I_0 + 2\dot{y}_1^3(0)(I_b - I_0) + \ddot{y}_1(0)(2G_b - 3G_0)(I_b - I_0)}{\dot{y}_1^2(0) + \dot{y}_1(0)(G_b - G_0)G_0(I_b - I_0)}\end{aligned} \tag{4.29}$$

and

$$p_5 = \frac{G_0(\ddot{y}_2(0)\dot{y}_2(0) + \dddot{y}_2(0)(I_b - I_0 - 2\dot{y}_1(0)\dot{y}_2(0)(I_b - I_0)))}{\ddot{y}_2(0)\dot{y}_2(0) + \dddot{y}_2(0)(I_b - I_0)}. \tag{4.30}$$

Thus Eqn. (4.29) implies that parameter p_2 is uniquely identifiable if I_b and G_b are known and Eqn. (4.30) implies that parameter p_5 is uniquely identifiable if I_b is known.

The fifth coefficients of the Taylor Series expansions and their evaluations at

$t = 0$ are given by

$$\begin{aligned} y_1^{(4)}(0) = &- G_0^2 p_3 p_4 - G_b p_1 (p_1^3 - 3p_3(p_2 + p_6)I_0 - I_b) \\ &+ 2p_1 p_3(-I_0 + I_b)) + G_0(p_1^4 - 4p_1 p_3(p_2 + p_6)(I_0 + I_b) \\ &+ 6p_1^2 p_3(I_0 + I_b) + p_3(p_4 p_5 - (I_0 - I_b)(p_2^2 + p_2 p_6 \\ &+ p_6^2 - 3p_3 I_0 + 3p_3 I_b))) \end{aligned} \tag{4.31}$$

and

$$\begin{aligned} y_2^{(4)}(0) = &- p_6(2(-G_0 p_1 + G_b p_1)p_4 - p_6(p_4(G_0 - p_5) + p_6^2(I_0 - I_b))) \\ &+ 3p_4(-p_1(-G_0 p_1 + G_b p_1) - G_0 p_3(I_0 - I_b) \end{aligned}$$

whereby

$$I_b = \frac{\ddot{y}_2(0)\dot{y}_2(0)(3\ddot{y}_1(0) + 2\dot{y}_1(0)) - 3\dddot{y}_2(0)\ddot{y}_1(0)y_2(0) + 2y_2^{(4)}(0)\dot{y}_1(0)y_2(0)}{-3\dddot{y}_2(0)\ddot{y}_1(0) + 2y_2^{(4)}(0)\dot{y}_1(0)}. \tag{4.32}$$

By using the **Solve** command within Mathematica [Wolfram, 1996], two sets of solutions can be obtained from Eqn. (4.31) for the parameter G_b, therefore no conclusive result on the identifiability of G_b can be drawn. The evaluations for G_b are relatively large and are not included in this text for brevity. However, Eqn. (4.32) implies that parameter I_b is uniquely identifiable.

As the initial condition for insulin is given by

$$I_0 = p_7 + I_b \ ,$$

therefore, if I_b (Eqn. (4.32)) and I_0 (Eqn. (4.24)) are identifiable then, the parameter p_7 is also identifiable. Therefore the parameters p_4, p_5 and p_6 are uniquely identifiable without any constraint or *a priori* knowledge. Higher

order coefficients do not permit further information or solutions for G_b. However, it is clear that, if the parameter G_b is known, then the EMM over the pre-switching phase is structurally globally identifiable.

Subsequent to this analysis which showed that *a priori* knowledge was required in order to establish global identifiability of the remaining parameters, application of the Similarity Transformation approach was considered to establish whether additional information could be obtained.

4.5 Structural Identifiability of the EMM Over the Pre-Switching Phase Using the Similarity Transformation Approach

A structural identifiability analysis of the EMM over the pre-switching phase is tested using the Similarity Transformation approach [Vajda et al., 1989; Evans et al., 2002] as results obtained with the Taylor Series approach were not totally conclusive.

From a structural identifiability analysis perspective, the Similarity Transformation approach is not immediately applicable because of the time term in the insulin differential equation; the system is not strictly in the standard state space form required. In order to perform a structural identifiability analysis for the EMM using this approach, a new state variable is introduced to represent the time term, thus generating an augmented model, but one in the required form. This is achieved by setting the additional "dummy" variable as:

$$R(t) = t$$

whereby

$$\dot{R}(t) = 1.$$

This augments the number of state space variables by one, adding an additional differential equation to the state space model, but the augmented system is now in the state space form required for application of the Similarity Transformation approach [Vajda et al., 1989]. However, this augmented system is not controllable, and so the version of the Similarity Transformation approach for uncontrolled nonlinear systems is therefore applied [Evans et al., 2002]. This approach was developed by Evans et al. [2002] and applied under the constraint that the impulsive Intravenous Glucose Tolerance Test (IVGTT) input is alternatively considered as a non-zero initial condition for the system.

Therefore, the system equations for the augmented version of the EMM are given by:

$$\dot{G}(t) = -[p_1 + X(t)]G(t) + p_1 G_b \tag{4.33}$$

$$\dot{X}(t) = -p_2 X(t) + p_3[I(t) - I_b] \tag{4.34}$$

$$\dot{I}(t) = p_4 R[G(t) - p_5] - p_6[I(t) - I_b] \tag{4.35}$$

$$\dot{R}(t) = 1 \tag{4.36}$$

with observations

$$y_1(t) = G(t) \tag{4.37}$$

$$y_2(t) = I(t) \tag{4.38}$$

and initial conditions given by

$$G(0) = G_0 \tag{4.39}$$

$$X(0) = 0 \tag{4.40}$$

$$I(0) = I_0 \tag{4.41}$$

$$R(0) = 0. \tag{4.42}$$

The analysis is then carried out using Theorem 3.1.5 [Evans et al., 2002]. The observability rank criterion (ORC) for the model is analysed initially. First, consider

$$\mu_1(\boldsymbol{x}) = G(t)$$

then choose

$$\begin{aligned}\mu_2(\boldsymbol{x}) &= L_{fp}\mu_1(\boldsymbol{x}) \\ &= -[p_1 + X(t)]G(t) + p_1 G_b.\end{aligned}$$

Then consider

$$\mu_3(\boldsymbol{x}) = I(t)$$

and choose

$$\begin{aligned}\mu_4(\boldsymbol{x}) &= L_{fp}\mu_3(\boldsymbol{x}) \\ &= p_4 R[G(t) - p_5] - p_6[I(t) - I_b].\end{aligned}$$

Suppose that

$$H(\boldsymbol{x}, \boldsymbol{p}) = [\mu_1(\boldsymbol{x}, \boldsymbol{p}), \mu_2(\boldsymbol{x}, \boldsymbol{p}), \mu_3(\boldsymbol{x}, \boldsymbol{p}), \mu_4(\boldsymbol{x}, \boldsymbol{p})]^T$$

then

$$\frac{\partial H_p(\boldsymbol{x})}{\partial \boldsymbol{x}} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ p_1 & G_0 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ p_4 R & 0 & -p_6 & p_4(G_0 - p_5) \end{bmatrix}.$$

The four (row) vectors in this matrix are (generically) linearly independent, therefore, the ORC is satisfied.

Next, the structural identifiability analysis is performed.

Let $V_{\bar{\boldsymbol{p}}} = W$, where $\bar{\boldsymbol{p}} = (\bar{p}_1, ..., \bar{p}_6)^T$, and $\tau > 0$ be such that $\boldsymbol{x}(t, \bar{\boldsymbol{p}}) \in W$ for all $t \in [0, \tau)$. For λ to satisfy Eqn. (3.22), it is necessary that

$$\begin{bmatrix} 1 & 0 & 1 & 0 \end{bmatrix} \begin{bmatrix} \lambda_1(\boldsymbol{x}) \\ \lambda_2(\boldsymbol{x}) \\ \lambda_3(\boldsymbol{x}) \\ \lambda_4(\boldsymbol{x}) \end{bmatrix} = \begin{bmatrix} 1 & 0 & 1 & 0 \end{bmatrix} \begin{bmatrix} G \\ X \\ I \\ R \end{bmatrix}.$$

Therefore,

$$\lambda_1(\boldsymbol{x}) = G$$

and

$$\lambda_3(\boldsymbol{x}) = I,$$

hence

$$\frac{\partial \lambda_1(\boldsymbol{x})}{\partial G} = \frac{\partial \lambda_3(\boldsymbol{x})}{\partial I} = 1$$

and

$$\frac{\partial \lambda_1(\boldsymbol{x})}{\partial X} = \frac{\partial \lambda_1(\boldsymbol{x})}{\partial I} = \frac{\partial \lambda_1(\boldsymbol{x})}{\partial R} = \frac{\partial \lambda_3(\boldsymbol{x})}{\partial G} = \frac{\partial \lambda_3(\boldsymbol{x})}{\partial X} = \frac{\partial \lambda_3(\boldsymbol{x})}{\partial R} = 0.$$

After rearrangement Eqn. (3.21) is then given by

$$\boldsymbol{f}(\lambda(\boldsymbol{x}(t, \bar{\boldsymbol{p}})), \boldsymbol{p}) = \begin{bmatrix} 1 & 0 & 0 & 0 \\ \frac{\partial \lambda_2}{\partial G} & \frac{\partial \lambda_2}{\partial X} & \frac{\partial \lambda_2}{\partial I} & \frac{\partial \lambda_2}{\partial R} \\ 0 & 0 & 1 & 0 \\ \frac{\partial \lambda_4}{\partial G} & \frac{\partial \lambda_4}{\partial X} & \frac{\partial \lambda_4}{\partial I} & \frac{\partial \lambda_4}{\partial R}. \end{bmatrix} \boldsymbol{f}(\boldsymbol{x}(t, \bar{\boldsymbol{p}}), \bar{\boldsymbol{p}}). \tag{4.43}$$

The first component of Eqn. (4.43) is given by

$$\begin{aligned}\boldsymbol{f}_1(\lambda(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),\boldsymbol{p}) &= \mu_2(\lambda(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),\boldsymbol{p}) \\ &= \boldsymbol{f}_1(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) = \mu_2(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}).\end{aligned}$$

Then

$$-(p_1+\lambda_2)G + p_1G_b = -(\bar{p}_1+X)G + \bar{p}_1\bar{G}_b$$

which after rearranging yields

$$\lambda_2 = -p_1 + \bar{p}_1 + X + \frac{\bar{p}_1\bar{G}_b - p_1G_b}{G}. \tag{4.44}$$

Differentiation of Eqn. (4.44) with respect to the arguments gives

$$\frac{\partial\lambda_2}{\partial G} = \frac{\bar{p}_1\bar{G}_b - p_1G_b}{G^2}$$

$$\frac{\partial\lambda_2}{\partial X} = 1$$

and

$$\frac{\partial\lambda_2}{\partial I} = \frac{\partial\lambda_2}{\partial R} = 0.$$

The second component of Eqn. (4.43) is satisfied if and only if

$$\boldsymbol{f}_2(\lambda(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),\boldsymbol{p}) - \frac{\partial\lambda_2}{\partial G}\boldsymbol{f}_1(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) - \frac{\partial\lambda_2}{\partial X}\boldsymbol{f}_2(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) = 0 \tag{4.45}$$

whereby

$$\begin{aligned}&G(-G_bp_1p_2 + \bar{G}_b\bar{p}_1p_2 + G(p_1p_2 + \bar{p}_1p_2 + p_3I - p_3I_b - p_2X)) \\ &-\bar{G}_b\bar{p}_1(-G_bp_1 + \bar{G}_b\bar{p}_1) - G(G_bp_1 - \bar{G}_b\bar{p}_1)(\bar{p}_1 + X) \\ &-G^2(\bar{p}_3(I - \bar{I}_b) - \bar{p}_2X) = 0\end{aligned}$$

which satisfes Eqn. (4.45) and can be written in the form

$$\begin{aligned} q_0(\boldsymbol{p},\bar{\boldsymbol{p}}) + q_1(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}}) + q_2(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}})X(t,\bar{\boldsymbol{p}}) \\ +q_3(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}})^2 + q_4(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}})^2 I(t,\bar{\boldsymbol{p}}) \\ +q_5(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}})^2 X(t,\bar{\boldsymbol{p}}) = 0 \end{aligned}$$

for all $t \in [0,\tau)$, where

$$\begin{aligned} q_0(\boldsymbol{p},\bar{\boldsymbol{p}}) &= -G_b\bar{G}_b p_1\bar{p}_1 + \bar{G}_b^2\bar{p}_1^2 \\ q_1(\boldsymbol{p},\bar{\boldsymbol{p}}) &= -G_b p_1\bar{p}_1 + \bar{G}_b\bar{p}_1^2 - G_b p_1 p_2 + \bar{G}_b\bar{p}_1 p_2 \\ q_2(\boldsymbol{p},\bar{\boldsymbol{p}}) &= -G_b p_1 + \bar{G}_b\bar{p}_1 \\ q_3(\boldsymbol{p},\bar{\boldsymbol{p}}) &= \bar{I}_b\bar{p}_3 + p_1 p_2 - \bar{p}_1 p_2 - I_b p_3 \\ q_4(\boldsymbol{p},\bar{\boldsymbol{p}}) &= -\bar{p}_3 + p_3 \\ q_5(\boldsymbol{p},\bar{\boldsymbol{p}}) &= \bar{p}_2 - p_2. \end{aligned}$$

This polynomial must be identically zero. Therefore each of its coefficient must be zero for all ($t \in [0,\tau)$) hence

$$q_0(\boldsymbol{p},\bar{\boldsymbol{p}}) = q_1(\boldsymbol{p},\bar{\boldsymbol{p}}) = q_2(\boldsymbol{p},\bar{\boldsymbol{p}}) = q_3(\boldsymbol{p},\bar{\boldsymbol{p}}) = q_4(\boldsymbol{p},\bar{\boldsymbol{p}}) = q_5(\boldsymbol{p},\bar{\boldsymbol{p}}) = 0.$$

Solving this system of algebraic equations, it can be concluded that

$$p_2 = \bar{p}_2 \tag{4.46}$$

$$p_3 = \bar{p}_3 \tag{4.47}$$

$$G_b p_1 = \bar{G}_b\bar{p}_1 \tag{4.48}$$

$$p_1 p_2 - \bar{p}_1 p_2 = p_3 I_b - \bar{p}_3\bar{I}_b. \tag{4.49}$$

The third component of Eqn. (4.43) gives

$$\begin{aligned} \boldsymbol{f}_3(\lambda(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),\boldsymbol{p}) &= \mu_4(\lambda(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),\bar{\boldsymbol{p}}) \\ &= \boldsymbol{f}_3(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) = \mu_4(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) \end{aligned} \tag{4.50}$$

which gives

$$p_4\lambda_4(G-p_5) - p_6(I-I_b) = \bar{p}_4 R(G-\bar{p}_5) - \bar{p}_6(I-\bar{I}_b)$$

and after rearranging this yields

$$\lambda_4 = \frac{\bar{p}_4 R(G-\bar{p}_5) - \bar{p}_6(I-\bar{I}_b) + p_6(I-I_b)}{p_4(G-p_5)}. \tag{4.51}$$

Differentiating Eqn. (4.51) with respect to the arguments gives

$$\begin{aligned} \frac{\partial\lambda_4}{\partial G} &= \frac{\bar{p}_4 R(p_5-\bar{p}_5) - \bar{p}_6(I-\bar{I}_b) + p_6(I-I_b)}{p_4(G-p_5)^2} \\ \frac{\partial\lambda_4}{\partial X} &= 0 \\ \frac{\partial\lambda_4}{\partial I} &= \frac{p_6-\bar{p}_6}{p_4(G-p_5)} \end{aligned}$$

and

$$\frac{\partial\lambda_4}{\partial R} = \frac{\bar{p}_4(G_b-\bar{p}_5)}{p_4(G-p_5)}.$$

The fourth component of Eqn. (4.43) is satisfied if and only if

$$\begin{aligned} \boldsymbol{f}_4(\lambda(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),p) - \frac{\partial\lambda_4}{\partial G}\boldsymbol{f}_1(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) - \frac{\lambda_4}{\partial I}\boldsymbol{f}_3(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) \\ -\frac{\lambda_4}{\partial R}\boldsymbol{f}_4(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) = 0. \end{aligned} \tag{4.52}$$

Therefore, it can be written in the form

$$\begin{aligned} w_0(t,\bar{\boldsymbol{p}}) + w_1(t,\bar{\boldsymbol{p}})G(\boldsymbol{p},\bar{\boldsymbol{p}}) + w_2(t,\bar{\boldsymbol{p}})I(\boldsymbol{p},\bar{\boldsymbol{p}}) + w_3(t,\bar{\boldsymbol{p}})R(\boldsymbol{p},\bar{\boldsymbol{p}}) \\ + w_4(t,\bar{\boldsymbol{p}})G(\boldsymbol{p},\bar{\boldsymbol{p}})X(\boldsymbol{p},\bar{\boldsymbol{p}}) + w_5(t,\bar{\boldsymbol{p}})G(\boldsymbol{p},\bar{\boldsymbol{p}})I(\boldsymbol{p},\bar{\boldsymbol{p}}) \\ + w_6(t,\bar{\boldsymbol{p}})G(\boldsymbol{p},\bar{\boldsymbol{p}})R(\boldsymbol{p},\bar{\boldsymbol{p}}) + w_7(t,\bar{\boldsymbol{p}})G(\boldsymbol{p},\bar{\boldsymbol{p}})X(\boldsymbol{p},\bar{\boldsymbol{p}})I(\boldsymbol{p},\bar{\boldsymbol{p}}) \\ + w_8(t,\bar{\boldsymbol{p}})G(\boldsymbol{p},\bar{\boldsymbol{p}})R(\boldsymbol{p},\bar{\boldsymbol{p}})X(\boldsymbol{p},\bar{\boldsymbol{p}}) \\ + w_9(t,\bar{\boldsymbol{p}})G(\boldsymbol{p},\bar{\boldsymbol{p}})^2 + w_{10}(t,\bar{\boldsymbol{p}})G(\boldsymbol{p},\bar{\boldsymbol{p}})^2R(\boldsymbol{p},\bar{\boldsymbol{p}}) = 0. \end{aligned}$$

for all $t \in [0,\tau)$ where

$$\begin{aligned} w_0(\boldsymbol{p},\bar{\boldsymbol{p}}) &= p_4p_4^2 - \bar{p}_4p_5\bar{p}_5 + \bar{G}_b\bar{p}_1\bar{p}_6\bar{I}_b + p_5p_6\bar{p}_6\bar{I}_b - \bar{G}_b\bar{p}_1p_6I_b - p_5\bar{p}_6^2\bar{I}_b \\ w_1(\boldsymbol{p},\bar{\boldsymbol{p}}) &= -2p_4p_5 + \bar{p}_4p_5 + \bar{p}_4\bar{p}_5 + \bar{p}_1p_6I_b - \bar{p}_1\bar{p}_6\bar{I}_b - p_6\bar{p}_6\bar{I}_b + \bar{p}_6^2\bar{I}_b \\ w_2(\boldsymbol{p},\bar{\boldsymbol{p}}) &= -p_5p_6\bar{p}_6 + p_5\bar{p}_6^2 + \bar{G}_b\bar{p}_1p_6 - \bar{G}_b\bar{p}_1\bar{p}_6 \\ w_3(\boldsymbol{p},\bar{\boldsymbol{p}}) &= -\bar{p}_4p_5\bar{p}_5p_6 + \bar{p}_4p_5\bar{p}_5\bar{p}_6 + \bar{G}_b\bar{p}_1\bar{p}_4p_5 - \bar{G}_b\bar{p}_1\bar{p}_4\bar{p}_5 \\ w_4(\boldsymbol{p},\bar{\boldsymbol{p}}) &= I_bp_6 - \bar{I}_b\bar{p}_6 \\ w_5(\boldsymbol{p},\bar{\boldsymbol{p}}) &= p_6\bar{p}_6 - \bar{p}_6^2 - \bar{p}_1p_6 + \bar{p}_1\bar{p}_6 \\ w_6(\boldsymbol{p},\bar{\boldsymbol{p}}) &= -\bar{p}_1\bar{p}_4p_5 + \bar{p}_1\bar{p}_4\bar{p}_5 - \bar{p}_4p_5\bar{p}_6 + \bar{p}_4p_5p_6 + \bar{p}_4\bar{p}_5p_6 - \bar{p}_4\bar{p}_5\bar{p}_6 \\ w_7(\boldsymbol{p},\bar{\boldsymbol{p}}) &= -p_6 + \bar{p}_6 \\ w_8(\boldsymbol{p},\bar{\boldsymbol{p}}) &= -\bar{p}_4p_5 + \bar{p}_4\bar{p}_5 \\ w_9(\boldsymbol{p},\bar{\boldsymbol{p}}) &= p_4 - \bar{p}_4 \\ w_{10}(\boldsymbol{p},\bar{\boldsymbol{p}}) &= -\bar{p}_4p_6 + \bar{p}_4\bar{p}_6. \end{aligned}$$

The polynomial must be identically zero. Therefore each of its coefficients must be zero for all ($t \in [0,\tau)$) hence

$$\begin{aligned} w_0(\boldsymbol{p},\bar{\boldsymbol{p}}) = w_1(\boldsymbol{p},\bar{\boldsymbol{p}}) = w_2(\boldsymbol{p},\bar{\boldsymbol{p}}) = w_3(\boldsymbol{p},\bar{\boldsymbol{p}}) = w_4(\boldsymbol{p},\bar{\boldsymbol{p}}) = w_5(\boldsymbol{p},\bar{\boldsymbol{p}}) \\ = w_6(\boldsymbol{p},\bar{\boldsymbol{p}}) = w_7(\boldsymbol{p},\bar{\boldsymbol{p}}) = w_8(\boldsymbol{p},\bar{\boldsymbol{p}}) = w_9(\boldsymbol{p},\bar{\boldsymbol{p}}) = w_{10}(\boldsymbol{p},\bar{\boldsymbol{p}}) = 0. \end{aligned}$$

Solving this system of algebraic equations, it can be concluded that

$$I_b = \bar{I}_b \tag{4.53}$$

$$\bar{p}_4 = p_4 \tag{4.54}$$

$$p_5 = \bar{p}_5 \tag{4.55}$$

$$p_6 = \bar{p}_6. \tag{4.56}$$

Substituting (4.53) into (4.49) gives

$$p_1 = \bar{p}_1. \tag{4.57}$$

Substituting (4.57) into (4.48) gives

$$G_b = \bar{G}_b. \tag{4.58}$$

This analysis shows that all parameters (including the basal levels) G_b and I_b are uniquely identifiable and therefore the EMM in this form is structurally globally identifiable for observations of glucose and insulin.

This implies that the generation of further Taylor Series coefficients for this same experiment may also yield the glucose basal level (G_b) as a uniquely identifiable parameter, but computational complexity of these coefficients hinders such analysis. =

4.6 Parameter Estimation

Parameter estimation was performed with greater confidence for the EMM as it has been shown to be structurally globally identifiable. The parameter estimation for the EMM is usually carried out in two stages. The first stage involves the use of two of the system equations Eqns. (4.3) and (4.4), with

plasma insulin concentrations acting as a forcing function; the second stage of the fitting process involves Eqns. (4.5a) and (4.5b) with glucose concentrations acting as the forcing function [Bergman et al., 1979; Bergman and Bowden, 1981].

Parameter estimation was subsequently carried out using available experimental data for IVGTT experiments provided by Professor Leon Aarons, School of Pharmacy and Pharmaceutical Sciences, Manchester University, United Kingdom [Mills, 2007]. In total 28 sets of IVGTT data were made available, where the majority of the data sets lasted for approximately 240 minutes, these are Subjects 1-5, 7, 10, 14, 15, 19, 21-22, 24 and 27; 3 data sets lasted approximately 180 minutes and these are Subjects 11-12, 23; 6 data sets lasted approximately 120 minutes and these are Subjects 6, 8-9, 13, 26, 28; 3 data sets lasted approximately 80 minutes (Subjects 17-18 and 25), one set of data lasted 41 minutes (Subject 16) and one lasted 60 minutes (Subject 20). Table 4.1 shows the data sets for all subjects, the total duration lasted and the total number of data points collected. On average, each data set contains 14 data points where glucose and insulin concentrations are both individually measured.

The data sets were provided without any in-depth information regarding the subjects and it is not possible to conclude if any of the individuals was healthy, diabetic or suffering from any other health issues. Some of the IVGTT data sets were clearly not suitable for fitting, as these data sets contain missing data, i.e. only glucose or insulin concentrations (not both) are recorded at certain times, (see the examples in Figures 4.1 and 4.2); there are incomplete data set (see for example Figure 4.2) as the IVGTT is considerably shorter compared to the other IVGTTs and the glucose-insulin responses were still high even when the IVGTT has finished; some had unusual glucose-insulin responses and therefore were not suitable for the purpose of parameter

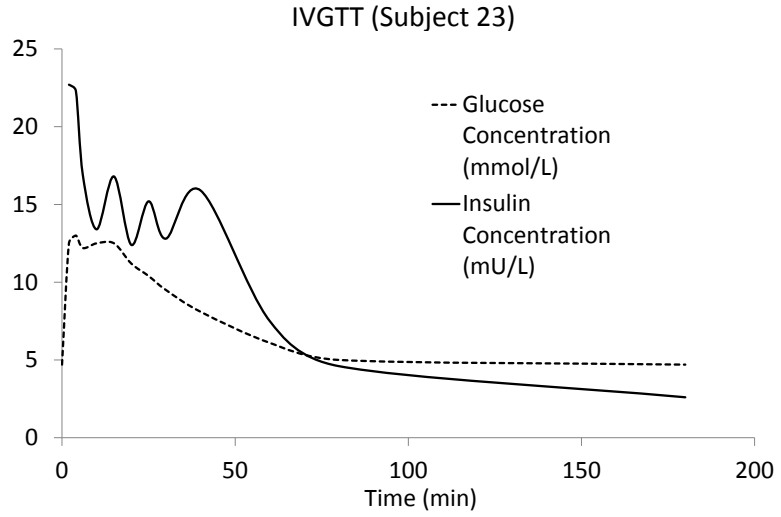

Figure 4.1: The IVGTT data set for Subject 23 contains missing data for insulin concentrations at the beginning of the IVGTT. Both glucose and insulin concentrations show non-typical IVGTT behaviour.

estimation (see for example Figures 4.1 and 4.3).

Parameter fitting was performed simultaneously for the full three-state EMM in one single step. This was performed by combining the insulin differential equations using appropriate sign functions. With this modification, the model will automatically switch from the pre-switching phase to the post-switching phase, and vice versa. The system equations are given by

$$\dot{G}(t) = -(p_1 + X(t))G(t) + p_1 G_b \tag{4.59}$$

$$\dot{X}(t) = -p_2 X(t) + p_3(I(t) - I_b) \tag{4.60}$$

$$\dot{I}(t) = p_4 t(G(t) - p_5) * sgn(sgn(G(t) - p_5) + 1) - p_6(I(t) - I_b) \tag{4.61}$$

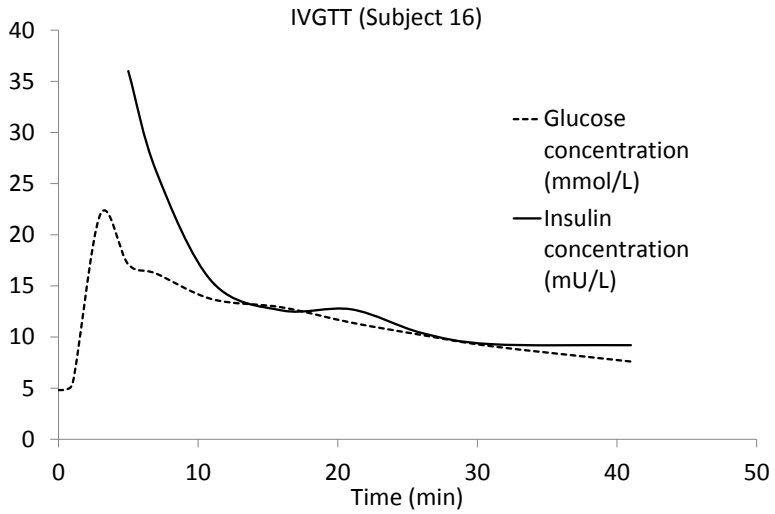

Figure 4.2: The IVGTT data set for Subject 16 contains missing data for insulin concentrations. This particular data set is also relatively short compared to the 27 other subjects.

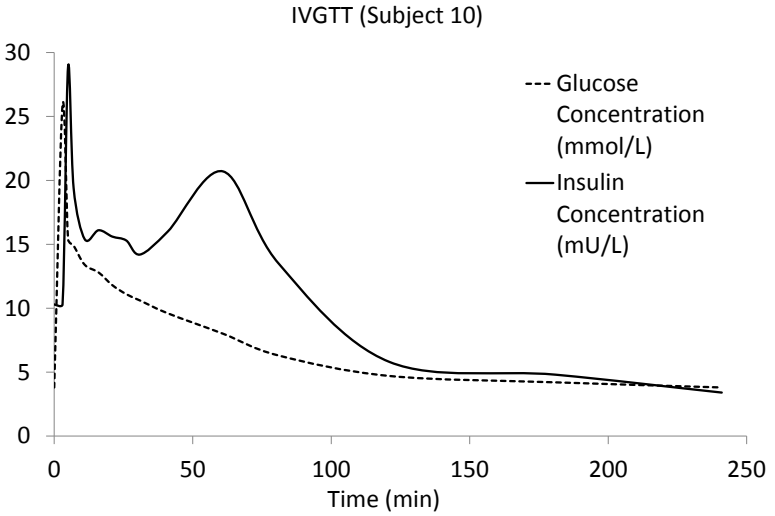

Figure 4.3: The IVGTT data set for Subject 10. The insulin dynamics show multiple irregular peaks and these are not typical of insulin dynamics for an IVGTT.

Subject	Duration (min)	NODP	Subject	Duration (min)	NODP
1	241	16	15	241	16
2	241	16	16	41	11
3	241	15	17	81	12
4	241	16	18	81	13
5	240	15	19	241	14
6	121	14	20	60	11
7	241	16	21	239	15
8	120	13	22	240	15
9	121	12	23	180	13
10	241	15	24	241	15
11	181	14	25	80	12
12	181	13	26	121	13
13	121	13	27	241	15
14	246	15	28	110	13

NODP represents number of data point

Table 4.1: Subjects and the duration of the corresponding IVGTT

and the initial conditions are given by

$$G(0) = G_0 \tag{4.62}$$

$$X(t) = 0 \tag{4.63}$$

$$I(0) = I_0 \tag{4.64}$$

and the parameters G_b and I_b are measurable with known values. These are usually the initial and/or final measurements of the glucose and insulin concentrations ($G_b \approx 5.0$ mmol/L and $I_b \approx 4.5$ mU/L), when glucose and insulin concentrations return to steady state. Therefore, only the parameters p_1, p_2, p_3, p_4, p_5 and p_6 are to be estimated.

The IVGTT data for Subjects 3, 8 and 17 are used for the parameter fitting. The data set for Subject 3 has a duration of 240 minutes and contains 16 data points for both glucose and insulin concentrations. The data set for Subject 8 is 120 minute IVGTT and contains 13 data points for both glucose and insulin concentrations. The data set for Subject 17 has a duration of 80

minutes and contains 12 data points for both glucose and insulin concentrations. All 3 sets of data show typical glucose-insulin responses to an IVGTT and therefore were considered suitable for the purpose of parameter estimation using the EMM.

Typical glucose-insulin dynamics behaviour for IVGTT is shown in Figure 2.7 where the glucose and insulin concentrations rise to peaks (first phase glucose-insulin action) after an input of glucose. The EMM only captures the decay of glucose-insulin concentrations after the peaks are reached (second phase glucose-insulin action) as shown in Figure 2.3. Therefore, the original data sets are altered for the purpose of the fitting. Table 4.2 show the augmented data sets where the data at the initial time $t = 0$ is when glucose and insulin concentrations are at their peak. Therefore, the altered data set for Subject 3 contains 13 data points; Subject 8 contains only 11 data points and for Subject 17 contains only 10 data points. The original data sets are shown in Appendix C.

Parameter estimation was carried out in FACSIMILE [AEA Technology, 1995], using the IVGTT data shown in Table 4.2. Table 4.3 shows a list of fits obtained, along with the data set used and the residual sum of squares (RSS) obtained within FACSIMILE . Fits 1-3 are performed using the data set for Subject 3, Fits 4-6 are performed using the data set for Subject 8 and Fits 7-9 are performed using the data set for Subject 17.

The parameter estimation performed shows that the determination of the parameters p_2 and p_3 proves challenging. The SDLN (the Standard Deviation for the Log-Normal distribution, used within FACSIMILE to guarantee non-negativity of parameter estimates) values for the parameters p_2 and p_3 in Fit 2 are 0.7182 and 1.2946; in Fit 3 are 0.9052 and 1.3405; in Fit 5 are 2.2899 and 1.5058 and in Fit 7 are 0.5688 and 0.8546. Fit 6 shows that the parameters p_2 and p_3 are undeterminable (no SDLN values generated as the

Subject 3					
Time (min)	Glucose (mmol/L)	Insulin (mU/L)	Time (min)	Glucose (mmol/L)	Insulin (mU/L)
0	18.3	79.0	28	9.4	14.2
2	17.3	71.2	38	7.7	10.9
4	15.9	50.3	58	5.8	4.7
8	14.6	34.0	78	5.1	3.0
13	12.7	25.9	178	5.4	3.0
18	11.3	20.4	238	5.7	4.3
23	10.0	16.8			

Subject 8					
Time (min)	Glucose (mmol/L)	Insulin (mU/L)	Time (min)	Glucose (mmol/L)	Insulin (mU/L)
0	15.2	49.3	26	10.7	14.0
2	14.7	42.1	36	9.2	14.5
6	13.7	26.9	56	7.4	11.2
11	12.6	20.4	76	5.9	6.6
16	11.9	18.4	116	4.5	3.2
21	11.3	16.9			

Subject 17					
Time (min)	Glucose (mmol/L)	Insulin (mU/L)	Time (min)	Glucose (mmol/L)	Insulin (mU/L)
0	14.8	42.1	21	10.7	13.0
2	14.4	31.8	26	10.0	12.6
6	14.1	18.6	36	8.8	12.4
11	12.8	14.5	56	6.6	7.2
16	11.8	13.2	76	5.6	4.6

Table 4.2: The IVGTT data for Subjects 3, 8 and 17.

Fit	Subject	RSS	Parameters determined
1	3	6.3258	$p_1, p_2, p_3, p_4, p_5, p_6$
2	3	$1.2285 \cdot 10$	$p_1, p_2, p_3, p_4, p_5, p_6$
3	3	6.0248	$p_1, p_2, p_3, p_4, p_5, p_6$
4	8	3.3173	$p_1, p_2, p_3, p_4, p_5, p_6$
5	8	3.2186	$p_1, p_2, p_3, p_4, p_5, p_6$
6	8	3.7108	p_1, p_4, p_5, p_6
7	17	1.3691	$p_1, p_2, p_3, p_4, p_5, p_6$
8	17	1.6247	p_1, p_3, p_4, p_5, p_6
9	17	0.8354	$p_1, p_2, p_3, p_4, p_5, p_6$
RSS represents the Residual Sum of Squares			

Table 4.3: List of Fits (1-9) for Subjects 3, 8 and 17 using the EMM and statistical information obtained within FACSMILE for each fits, i.e. the RSS (Residual Sum of Squares) and well determined parameters.

parameters are not well determined in FACSMILE) , and Fit 9 shows that the parameter p_2 is undeterminable, however, both sets produce reasonably good fits visually. This implies that determination of the insulin sensitivity index is difficult and unsatisfactory, as the key parameters needed to determine the insulin sensitivity index are p_2 and p_3.

From observations of the plots produced within FACSIMILE, or any other computational fitting packages, it is not possible to distinguish whether the fit was actually a "reasonable" fit, for example Fit 2 (see Figure A.2, Appendix A) produces visually plots that demonstrate a good fit to the glucose and insulin data with a relatively high residual sum of squares and Fits 6 and 8 (see Figures A.4 and A.6, Appendix A) do not have all of the parameters well determined. This demonstrates that parameter estimation must be carried out with careful analysis of the statistical information on the fit obtained within the tool used.

The parameter estimation also demonstrates that the establishment of the unique structural identifiability of a system does not guarantee a good fit to experimental data or a good fit with a unique vector of parameter values. There are several explanations as to why certain parameters are not

well determined; this could be due to the quality of the data, sampling, or other numerical identifiability issues, as well as the possible unsuitability of the structure of the EMM for such (typical) data sets.

It has proved challenging to improve the quality of the parameter estimates to achieve closer/tighter fits to the data used. Such difficulties have also been met by other researchers who have tried to improve numerical estimates of unknown parameters for IVGTT data by employing a variety of mathematical/statistical techniques, including Bayesian and Maximum Likelihood approaches [Pillonetto et al., 2003; Wilinska et al., 2005; Plank et al., 2006]. Alternatively, parameters in the models considered with lesser importance have been 'replaced' with constraints or externally estimated values in order to overcome numerical unidentifiability. However, there is the possibility that this could be avoided if sufficient information can be obtained at the *a priori* stage, possibly also permitting appropriate model reparameterisation via the structural analysis performed.

The best fit for Subjects 3, 8 and 17 are Fits 3, 5 and 9 respectively as the statistical information shows that these fits have the lowest RSS and that all the parameters were well determined with reasonable SDLN values. The SDLNs values for Fits 3, 8 and 17 are shown in Tables 4.4 and the Correlation Matrix of well-determined parameters are shown in Tables 4.5. The plots obtained from the parameter estimates for Fits 3, 5 and 9 are shown in Figures 4.4, 4.5 and 4.6 respectively. However, tighter fits with lower RSS and SDLNs for all the parameters would be more desirable.

The results for other fits, including Figures and Tables for SDLNs and Correlation Matrices are shown in Appendix A

	Fit 3 (Subject 3)		Fit 5 (Subject 8)		Fit 9 (Subject 17)	
Parameter	Value	[SDLN]	Value	[SDLN]	Value	[SDLN]
p_1	$3.148 \cdot 10^{-2}$	[0.443]	$1.998 \cdot 10^{-2}$	[0.203]	$9.000 \cdot 10^{-3}$	[0.825]
p_2	$6.814 \cdot 10^{-2}$	[0.905]	$1.443 \cdot 10^{-2}$	[2.209]	$4.925 \cdot 10^{-2}$	[0.473]
p_3	$3.276 \cdot 10^{-5}$	[1.341]	$7.168 \cdot 10^{-6}$	[1.506]	$7.785 \cdot 10^{-5}$	[0.589]
p_4	$1.350 \cdot 10^{-2}$	[0.365]	$8.348 \cdot 10^{-3}$	[0.153]	$1.477 \cdot 10^{-2}$	[0.073]
p_5	6.438	[0.135]	5.595	[0.060]	6.323	[0.029]
p_6	$1.178 \cdot 10^{-1}$	[0.067]	$1.023 \cdot 10^{-1}$	[0.049]	$1.718 \cdot 10^{-1}$	[0.029]
	RSS = 6.0248		RSS =3.2187		RSS = 0.83538	

Table 4.4: The SDLN values for Fit 3 (Subject 3), Fit 5 (Subject 8) and Fit 9 (Subject 17).

Fit 3 (Subject 3)						
Row/Column	p_1	p_2	p_3	p_4	p_5	p_6
p_1	1.000	-0.774	-0.966	0.017	0.124	-0.066
p_2	-0.774	1.000	0.899	0.101	-0.028	0.097
p_3	-0.966	0.899	1.000	0.031	-0.114	0.097
p_4	0.017	0.101	0.031	1.000	0.762	0.744
p_5	0.124	-0.028	-0.114	0.762	1.000	0.331
p_6	-0.066	0.097	0.097	0.744	0.331	1.000

Fit 5 (Subject 8)						
Row/Column	p_1	p_2	p_3	p_4	p_5	p_6
p_1	1.000	-0.863	-0.959	0.257	0.432	-0.002
p_2	-0.873	1.000	0.954	-0.098	-0.348	0.064
p_3	-0.959	0.954	1.000	-0.201	-0.473	0.041
p_4	0.257	-0.098	-0.201	1.000	0.620	0.716
p_5	0.432	-0.348	-0.473	0.620	1.000	0.161
p_6	-0.002	0.064	0.041	0.716	0.161	1.000

Fit 9 (Subject 17)						
Row/column	p_1	p_2	p_3	p_4	p_5	p_6
p_1	1.000	-0.955	-0.990	0.190	0.406	-0.075
p_2	-0.955	1.000	0.984	-0.055	-0.362	0.137
p_3	-0.990	0.984	1.000	-0.137	-0.412	0.118
p_4	0.190	-0.055	-0.137	1.000	0.575	0.629
p_5	0.406	-0.362	-0.412	0.575	1.000	0.028
p_6	-0.075	0.137	0.118	0.629	0.028	1.000

Table 4.5: The correlation matrix for the parameter estimates for Fit 3 (Subject 3), Fit 5 (Subject 8) and Fit 9 (Subject 17).

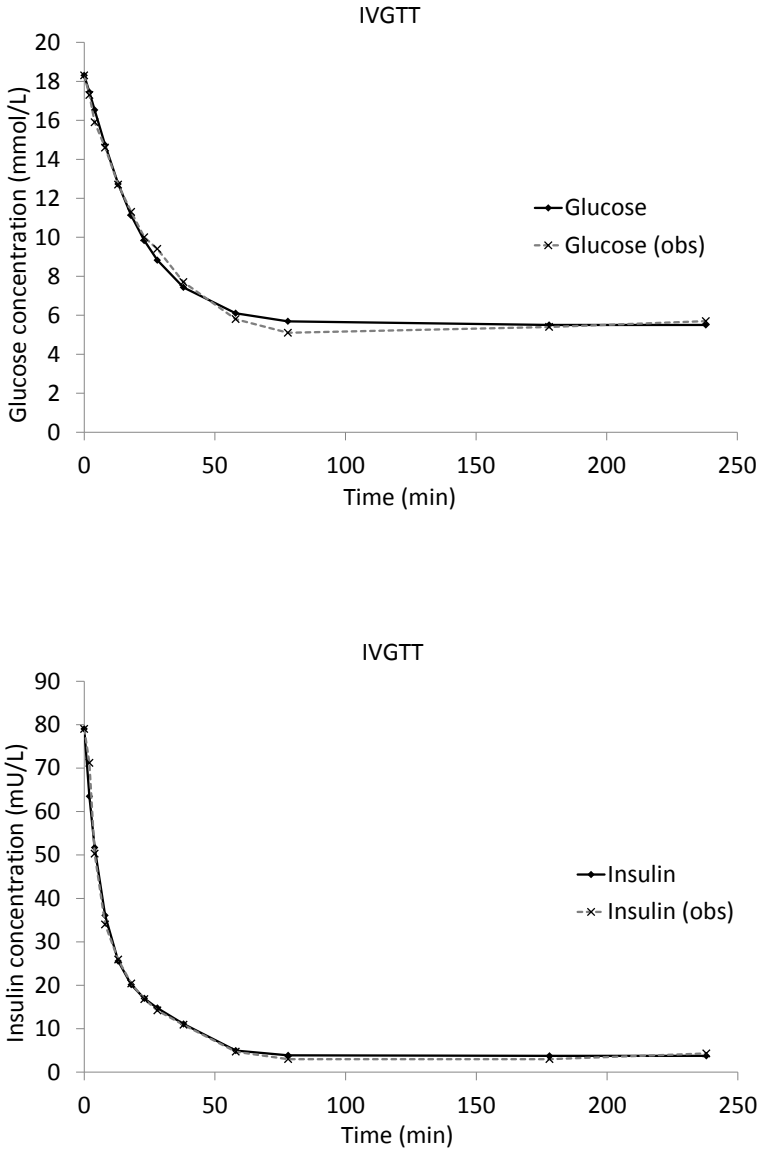

Figure 4.4: The parameter fitting of the EMM to the IVGTT glucose and insulin data for Fit 3 (Subject 3).

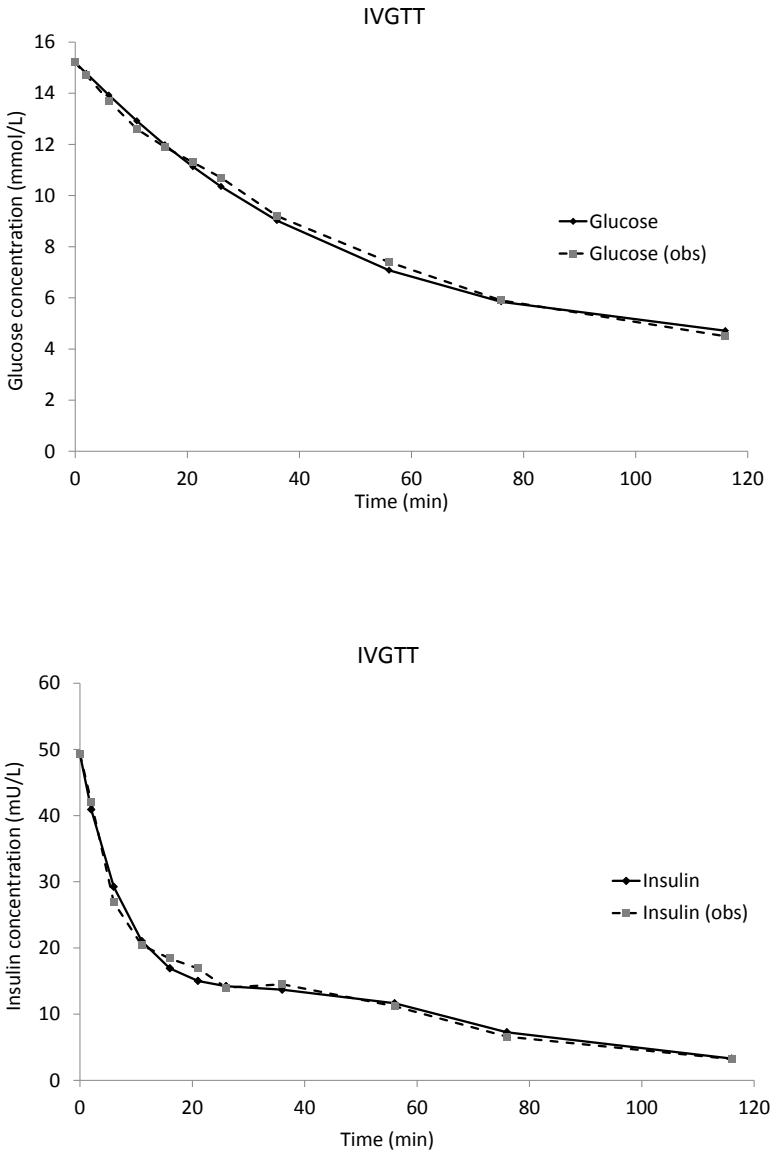

Figure 4.5: The parameter fitting of the EMM to the IVGTT glucose and insulin data for Fit 5 (Subject 8).

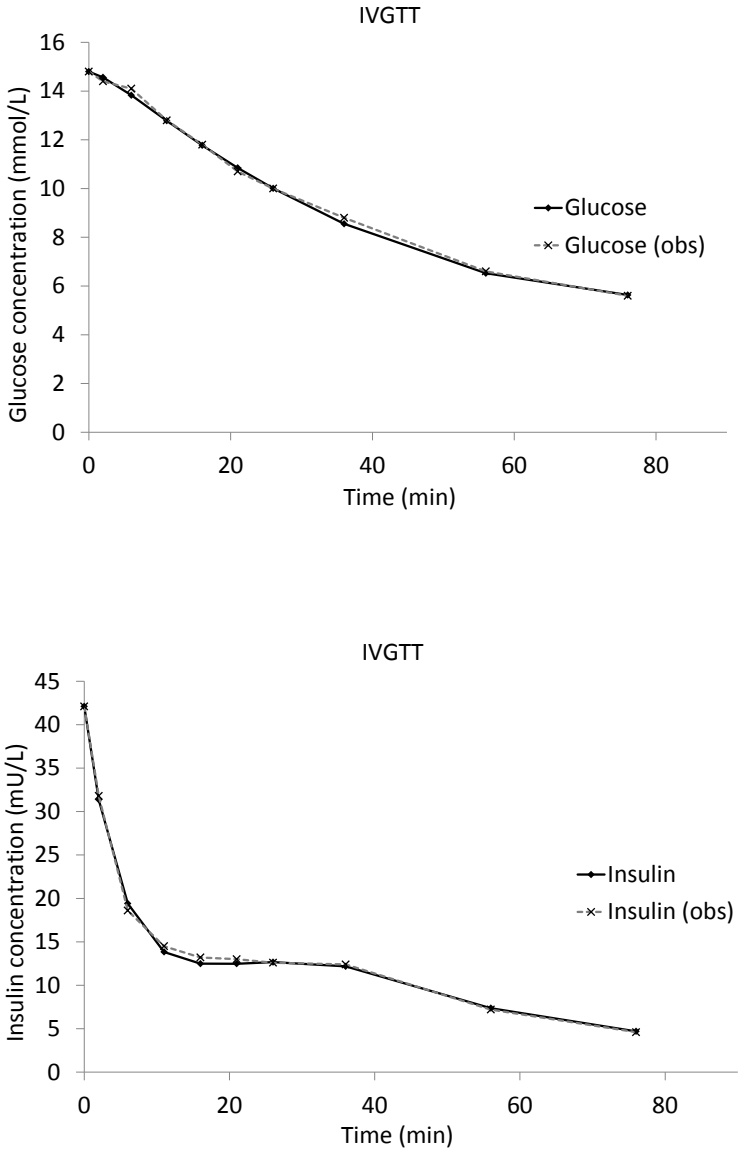

Figure 4.6: The parameter fitting of the EMM to the IVGTT glucose and insulin data for Fit 9 (Subject 17).

Chapter 5

Structural Identifiability of The Euglycemic Hyperinsulinemic Clamp Model

5.1 Structural Identifiability Analysis

The Euglycemic Hyperinsulinemic Clamp (EIC) is known as the "gold standard" for identifiying insulin sensitivity for an individual [DeFronzo et al., 1979; Vogel et al., 2006]. Picchini et al. [2005] developed a model that describes the oscillating behaviour of glucose-insulin dynamics during the course of the clamp. The model is believed to be the first published model for EIC and such a model is an important contribution to the study of glucose-insulin dynamics and insulin sensitivity of different groups of individuals, diabetes sufferers and animals. A structural identifiability analysis is an essential step to determine whether the parameters in the EIC model are structurally identifiable.

The structural identifiability analysis for this model was carried out using the Taylor Series approach with the aid of the symbolic computational

tool, Mathematica [Wolfram, 1996] and (as in Chapter 2, Section 2.5) the system equations are given by:

$$\dot{G}(t) = \frac{T_{gx}[t-\tau_g] + T_{gh}(t)}{V_g} - \frac{T_{xg}G(t)}{0.1+G(t)} - K_{xgI}G(t)I(t) \tag{5.1}$$

$$\dot{I}(t) = \frac{T_{iG}G(t) + T_{ix}(t)}{V_i} - K_{xi}I(t) \tag{5.2}$$

where

$$T_{gh}(t) = T_{ghmax}\exp(-\lambda G(t)I(t)) \tag{5.3}$$

and the initial conditions are given by

$$T_{gh}(0) = T_{ghb} = T_{ghmax}\exp(\lambda G_b I_b)$$

$$G(0) = G_b$$

$$I(0) = I_b.$$

The EIC model contains two observable variables, glucose and insulin plasma concentrations, normally with two piecewise constant input functions $T_{gx}(t)$ and $T_{ix}(t)$. For the analysis performed (relative to the experimental data available where no inputs of insulin were provided) it was assumed that $T_{ix}(t) = 0$ for all time. In addition $T_{gx}(t)$ was assumed to be known and constant over the time period considered. There is a total of eight unknown parameters to be identified through the observations,

$$\boldsymbol{p} = [T_{gh}, T_{ghmax}, V_g, V_i, T_{xg}, K_{xgI}, T_{iG}, K_{xi}, \lambda]. \tag{5.4}$$

The assumptions made for this system are that the concentration of plasma glucose and insulin are observable, or measurable, and glucose inputs to the system are known during the analysis (i.e. piecewise constant infusions at

known levels). The observations of the system are therefore given by

$$y_1(t) = G(t)$$

and

$$y_2(t) = I(t).$$

The first coefficients of the Taylor Series expansions at $t = 0$ give

$$y_1(0) = G_b$$

and

$$y_2(0) = I_b.$$

The second coefficients of the Taylor Series expansions at $t = 0$ give

$$\dot{y}_1(0) = -\frac{G_b T_{xg}}{0.1 + G_b} + \frac{T_{ghmax} \exp(-\lambda G_b I_b)}{V_g} - I_b G_b K_{xgI}$$

and

$$\dot{y}_2(0) = \frac{G_b T_{iG}}{V_i} - K_{xi} I_b.$$

The third coefficients of the Taylor Series expansions at $t = 0$ give

$$\ddot{y}_1(0) = - K_{xgI} G_b \dot{y}_2(0) - \frac{T_{xg} G_b \dot{y}_1(0)}{(0.1 + G_b)^2} - \frac{T_{xg} \dot{y}_1(0)}{0.1 + G_b} + K_{xgI} I_b \dot{y}_1(0)$$

$$- \frac{\lambda T_{ghmax} \exp(-\lambda G_b I_b)(I_b \dot{y}_1(0) + G_b \dot{y}_2(0))}{V_g}$$

and

$$\ddot{y}_2(0) = -K_{xi} \dot{y}_2(0) + \frac{T_{iG} \dot{y}_1(0)}{V_i}.$$

The fourth coefficients of the Taylor Series expansions at $t = 0$ give

$$\dddot{y}_1(0) = -2K_{xgI}\dot{y}_1(0)\dot{y}_2(0) - K_{xgI}G_b\ddot{y}_2(0) - K_{xgI}I_b\ddot{y}_1(0)$$

$$-\frac{2T_{xg}G_b\dot{y}_1^2(0)}{(0.1+G_b)^3} + \frac{2T_{xg}\dot{y}_1^2(0)}{(0.1+G_b)^2} + \frac{G_bT_{xg}\ddot{y}_1(0)}{(0.1+G_b)^2} - \frac{T_{xg}\ddot{y}_1(0)}{0.1+G_b}$$

$$+\frac{T_{ghmax}\exp(-\lambda G_bI_b)(-\lambda G_b\dot{y}_2(0) - \lambda I_b\dot{y}_1(0))^2}{V_g}$$

$$+\frac{T_{ghmax}\exp(-\lambda G_bI_b)(-2\lambda\dot{y}_1(0)\dot{y}_2(0) - \lambda G_b\ddot{y}_2(0) - \lambda I_b\ddot{y}_1(0))}{V_g}$$

and

$$\dddot{y}_2(0) = -K_{xi}\ddot{y}_2(0) + \frac{T_{iG}\ddot{y}_1(0)}{V_i}.$$

The fifth coefficients of the Taylor Series expansions at $t = 0$ give

$$y_1^{(4)}(0) = -3K_{xgI}\dot{y}_1(0)\ddot{y}_2(0) - 3K_{xgI}\dot{y}_2(0)\ddot{y}_1(0) - K_{xgI}G_b\dddot{y}_2(0)$$

$$- K_{xgI}I_b\dddot{y}_1(0) + \frac{6G_bT_{xg}\dot{y}_1^3(0)}{(0.1+G_b)^4} - \frac{6T_{xg}\dot{y}_1^3(0)}{(0.1+G)^3} + \frac{T_{xg}G_b\dddot{y}_1(0)}{(0.1+G_b)^2}$$

$$-\frac{6T_{xg}G_b\dot{y}_1(0)\ddot{y}_1(0)}{(0.1+G_b)^3} + \frac{6T_{xg}\dot{y}_1(0)\ddot{y}_1(0)}{(0.1+G_b)^2} - \frac{T_{xg}\dddot{y}_1(0)}{0.1+G_b}$$

$$-\frac{\lambda T_{ghmax}\exp(\lambda G_bI_b)(G_b\dot{y}_2(0) + I_b\dot{y}_1(0))^3}{V_g}$$

$$-\frac{3\lambda T_{ghmax}\exp(-\lambda G_bI_b)}{V_g}\Big(-\lambda I_b\dot{y}_1(0) - G_b\lambda\dot{y}_2(0)\Big)$$

$$\times\Big(-2\lambda\dot{y}_1(0)\dot{y}_2(0) - \lambda I_b\ddot{y}_1(0) - G_b\lambda\ddot{y}_2(0)\Big)$$

$$+\frac{T_{ghmax}\exp(-\lambda G_bI_b)}{V_g}$$

$$\times(-3\lambda\dot{y}_1(0)\ddot{y}_2(0) - 3\lambda\dot{y}_2(0)\ddot{y}_1(0) - \lambda G_b\dddot{y}_2(0) - \lambda I_b\dddot{y}_1(0))$$

and

$$\dddot{y}_2(0) = K_{xi}\dddot{y}_2(0) + \frac{T_{iG}\dddot{y}_1(0)}{V_i}.$$

The sixth coefficients of the Taylor Series expansions at $t = 0$ give

$$y_1^{(5)}(0) = -\frac{24G_bT_{xg}\dot{y}_1^4(0)}{(0.1+G_b)^5} + \frac{24T_{xg}\dot{y}_1^4(0)}{(0.1+G_b)^4} + \frac{36G_bT_{xg}\dot{y}_1^2(0)\ddot{y}_1(0)}{(0.1+G_b)^4} - \frac{36T_{xg}\dot{y}_1^2(0)\ddot{y}_1(0)}{(0.1+G_b)^3}$$

$$+\frac{\exp(-\lambda G_bI_b)T_{ghmax}(-\lambda I_b\dot{y}_1(0) - G_b\lambda\dot{y}_2(0))^4}{V_g} - \frac{6G_bT_{xg}\ddot{y}_1^2(0)}{(0.1+G_b)^3}$$

$$-\frac{6T_{xg}\ddot{y}_1^2(0)}{(0.1+G_b)^2} - 6K_{xgI}\ddot{y}_1(0)\ddot{y}_2(0) + \frac{8G_bT_{xg}\dot{y}_1(0)\dddot{y}_1(0)}{(0.1+G_b)^3}$$

$$+\frac{T_{xg}\dot{y}_1(0)\dddot{y}_3(0)}{(0.1+G_b)^2} + \frac{6\exp(-\lambda G_bI_b)T_{ghmax}}{V_g}(-\lambda I_b\dot{y}_1(0) - \lambda G_b\dot{y}_2(0))^2$$

$$\times(-2\lambda\dot{y}_1(0)\dot{y}_2(0) - \lambda I_b\ddot{y}_1(0) - G_b\lambda\ddot{y}_2(0))$$

$$+\frac{3\exp(-\lambda G_bI_b)T_{ghmax}(-2\lambda\dot{y}_1(0)\dot{y}_2(0) - \lambda I_b\ddot{y}_1(0) - \lambda G_b\ddot{y}_2(0))^2}{V_g}$$

$$-4K_{xgI}\dot{y}_2(0)\dddot{y}_1(0) - 4K_{xgI}\dot{y}_1(0)\dddot{y}_2(0) - K_{xgI}I_by_1^{(4)}(0)$$

$$-\frac{G_bT_{xg}y_1^{(4)}(0)}{(0.1+G_b)^2} - \frac{T_{xg}y^{(4)}(0)}{(0.1+G_b)} - G_bK_{xgI}y_2^{(4)}(0) + \frac{\exp(\lambda G_bI_b)T_{ghmax}}{V_g}$$

$$\times\lambda(-6\ddot{y}_1(0)\ddot{y}_2(0) - 4\dot{y}_2(0)\dddot{y}_1(0) - 4\dot{y}_1(0)\dddot{y}_2(0) - I_by_1^{(4)}(0) - G_by_2^{(4)}(0))$$

$$+\frac{4\exp(-\lambda G_bI_b)T_{ghmax}}{V_g}(-\lambda I_b\dot{y}_1(0) - \lambda G_b\dot{y}_2(0))$$

$$\times(-3\lambda\dot{y}_2(0)\ddot{y}_1(0) - 3\lambda\dot{y}_1(0)\ddot{y}_2(0) - \lambda I_b\dddot{y}_1(0) - \lambda G_b\dddot{y}_2(0))$$

and

$$y_2^{(5)}(0) = K_{xi}y_2^{(4)}(0) + \frac{T_{iG}y_1^{(4)}(0)}{V_i}.$$

By using the **Solve** command up to and including the sixth Taylor Series coefficients within Mathematica, it can be shown that, if, for example, the parameters V_g and V_i are known, then all other parameters can be uniquely identified. Alternatively, if instead the parameters T_{iG} and T_{ghb} are considered known then all other parameters are uniquely identifiable.

Since blood sampling gives information on glucose and insulin concentrations it allows us to estimate the distribution volume of glucose and insulin

(i.e. V_g and V_i, respectively). Hence, with these parameters estimable (known) the model is structurally globally identifiable. However, if, in practice these two parameters cannot be well determined from the experiments performed then this obviously creates a problem.

Picchini et al. [2005] state that parameters T_{iG} and T_{ghb} are determinable from steady state conditions. Thus this pairing of parameters may be more appropriate in terms of their *a priori* knowledge which may then permit more robust numerical parameter estimation.

This analysis has demonstrated that the model can subsequently be used with greater confidence for parameter estimation using glucose and insulin observation data. However, the quality and/or accuracy of estimates obtained may be limited in practice due to data quality and other numerical identifiability issues.

5.2 Parameter Estimation

For a glycemic clamp experiment, glucose alone is first infused into each subject at a level higher than normal blood glucose concentration. Glucose and insulin concentrations are measured frequently throughout the experiment and the higher glucose level is maintained by varying the glucose infusion rate. The clamp data were provided by Professor Leon Aarons, School of Pharmacy and Pharmaceutical Sciences, Manchester University, United Kingdom [Mills, 2007] as in Chapter 2.

Since the clinical data made available to this thesis only involve glycemic clamp data, in order to apply the available data, a slightly modified version of the EIC model is considered, where the insulin infusion term $T_{ix}(t)$ is removed (or $T_{ix}(t) = 0$), and the system equations are therefore given by

$$\dot{G}(t) = \frac{T_{gx}(t) + T_{ghmax}\exp(-\lambda G(t)I(t))}{V_g} - \frac{T_{xg}G(t)}{0.1 + G(t)} - K_{xgI}G(t)I(t) \quad (5.5)$$

$$\dot{I}(t) = \frac{T_{iG}G(t)}{V_i} - K_{xi}I(t) \quad (5.6)$$

and the initial conditions are given by

$$G(0) = G_b \quad (5.7)$$

$$I(0) = I_b \quad (5.8)$$

The system with Eqns. (5.5) and (5.6) is structural globally identifiable, as the structural identifiability analysis for the EIC model assumes that $T_{ix}(t) = 0$. Therefore, the model is globally structural identifiable with glucose infusion alone. The parameter estimation for the EIC model for the glycemic clamp data was carried out within FACSIMILE [AEA Technology, 1995]. The parameters G_b and I_b are assumed to be the initial or final glucose and insulin concentrations of the data sets ($G_b \approx 5.0$ mmol/L and $I_b \approx 4.5$ mU/L), therefore the parameter estimation for these two parameters was not required.

Data sets for Subjects 3, 8 and 17 (as shown in Table 5.1) were chosen, as the IVGTT data sets for these subjects were also used previously for the parameter estimations of the EMM. Table 5.2 shows a list of parameter estimations carried out using the glucose clamp data for Subjects 3, 8 and 17. Therefore, parameter estimates for the EIC model using these data, if any, may give further information of these subjects.

The parameter estimates generated within FACSMILE show that the EIC model is able to generate a similar glucose response occurring during a glycemic clamp experiment. However, corresponding simulation responses using the fitted parameters to the insulin observations do not give such good

agreement. They produce a typical insulin dynamic for a EIC experiment as shown in Figure 2.6.

The best set of parameter fits for Subject 3 is Fit 1 as 7 parameters are well determined, and only one parameter is not well determined. Although Fit 3 has the lowest RSS, only 6 parameters are determined. The SDLN values and the correlation matrix for the well determined parameters for Fit 1 are shown in Tables 5.3 and 5.4 respectively and the corresponding glucose-insulin responses are shown in Figure 5.1. The parameters appear to have high SDLN values; parameter T_{ghmax} has the lowest SDLNs value at 0.729, and the parameter T_{iG} at 1.110. The correlation matrix generated within Facsmile shows a moderate correlation between the parameter estimates with, in particular, a correlation of 0.824 between T_{xi} and V_g, -0.717 between V_i and K_{xgI}, 0.633 between T_{iG} and K_{xi}, 0.628 between λ and T_{ghmax} and 0.612 between T_{iG} and V_i. Fits 2 and 4 (Subject 3) may appear to have a visually tighter fit, however only 5 parameters are well determined and the SDLN value for the parameters are generally higher than 1, see Figures B.1, B.2 and B.3 and Tables B.1, B.4 in Appendix B.

The best set of parameter estimates for Subject 8 is Fit 7, where only one of the parameters are not well determined and it has the smallest RSS value compared to other fits using the same data set. The SDLN and the correlation matrix of the well determined parameters are shown in Table 5.3 and 5.4 and Figure 5.2 shows the corresponding plots produced for Fit 7. The SDLN values for the parameters are relatively high; parameter V_i at 1.400; T_{ghmax} at 1.317; T_{iG} at 0.980; K_{xgI} at 0.789 and the rest of the parameters over 0.362. The correlation generated within the FACSIMILE shows a high correlation between the parameters V_i and T_{iG} at 0.970, T_{ghmax} and K_{xi} at 0.924, λ and K_{xi} at 0.944, λ and T_{ghmax} at 0.936 and T_{ghmax} and V_i at -0.967. Results for Fits 5 and 6 are shown in Appendix B.

The best set of parameter estimates for Subject 17 is Fit 10 as only one of all the parameters are not well determined and the RSS is lowest at 1.6829×10^2. The SDLN of Fit 10 is shown in Table 5.3 and the correlation matrix of the well determined parameters is shown in Table 5.4. Figure 5.3 shows the glucose-insulin responses of Fit 10. Other results obtained for Subject 17, i.e. Fits 8 and 9, are included in Appendix B.

The parameter estimates demonstrate that the parameter T_{xg} is not determinable (in all Fits performed), possibly because the EIC model is designed to produce steady state insulin response as shown in Figure 2.6. This may also explain the high SDLNs and RSS values obtained for the Fits and therefore the EIC model, is not an appropriate model for the modelling of insulin responses of the glycemic clamp data.

This again demonstrates that the establishment of unique structural identifiability of a model does not guarantee a good fit to 'any kind' of experimental data. The parameter estimates demonstrate that the deterministic EIC model does not necessarily capture the transient dynamics in the glycemic data. Indeed none of the parameter estimates are particularly well determined in terms of the SDLNs generated. This model was developed to describe the oscillation of glucose-insulin dynamics during a EIC experiment and has also been extended and applied in a stochastic format by Picchini et al. [2006] in order to fully capture these transient dynamics. Picchini et al. [2008] have also simplified the model and applied a Maximum Likelihood approach to parameter estimation using clamp data.

Subject 3					
Time (min)	Glucose (mmol/L)	Insulin (mU/L)	Time (min)	Glucose (mmol/L)	Insulin (mU/L)
0	4.9	5.67	180	4.8	41.33
30	4.8	27.17	210	4.9	45.67
60	4.6	40.50	241	4.8	38.67
70	4.5	41.00	270	4.8	36.83
80	4.6	40.00	300	4.8	32.33
90	4.8	37.33	330	5.1	29.67
100	5.2	51.50	360	4.6	21.50
110	4.5	42.83	390	5.3	34.17
120	4.5	44.00	420	5.3	14.33
150	5.1	42.83			
Subject 8					
Time (min)	Glucose (mmol/L)	Insulin (mU/L)	Time (min)	Glucose (mmol/L)	Insulin (mU/L)
0	5.1	6.67	180	5.0	58.33
30	5.0	24.67	210	5.0	51.67
45	4.9	36.83	240	5.2	46.00
60	4.6	39.83	270	4.7	37.83
70	5.0	48.00	300	5.5	42.17
80	4.8	51.17	330	4.6	29.83
90	5.3	56.33	361	5.6	30.67
100	5.4	56.67	390	5.1	25.33
110	5.2	58.50	420	5.0	20.50
120	5.3	63.00	488	5.0	19.50
150	5.1	64.00			
Subject 17					
Time (min)	Glucose (mmol/L)	Insulin (mU/L)	Time (min)	Glucose (mmol/L)	Insulin (mU/L)
0	4.9	7.17	150	4.6	39.33
15	5.3	16.00	180	5.3	42.17
30	4.9	31.33	210	5.3	42.00
45	5.6	37.5	240	5.0	36.83
60	5.0	34.00	270	4.6	34.33
70	5.3	37.33	300	5.1	36.33
80	4.9	36.17	330	5.2	28.50
92	4.7	38.00	360	5.0	25.33
100	4.9	42.50	390	5.4	21.67
111	5.2	38.17	420	4.7	16.83
120	4.7	38.33	480	4.8	13.17

Table 5.1: The EIC data for subject 17.

Fit	Subject	RSS	Parameters determined
1	3	$2.2648 \cdot 10^2$	$K_{xgI}, K_{xi}, T_{iG}, T_{ghmax}, V_g, V_i, \lambda$
2	3	$2.2671 \cdot 10^2$	$K_{xgI}, K_{xi}, T_{ghmax}, V_i, \lambda$
3	3	$2.2524 \cdot 10^2$	$K_{xgI}, K_{xi}, T_{iG}, T_{ghmax}, V_g, \lambda$
4	3	$2.2585 \cdot 10^2$	$T_{iG}, T_{ghmax}, V_g, V_i, \lambda$
5	8	$4.0243 \cdot 10^2$	$K_{xgI}, K_{xi}, T_{iG}, T_{ghmax}, V_g, V_i$
6	8	$4.0167 \cdot 10^2$	$K_{xgI}, T_{iG}, T_{ghmax}, V_g, V_i, \lambda$
7	8	$3.9811 \cdot 10^2$	$K_{xgI}, K_{xi}, T_{iG}, T_{ghmax}, V_g, V_i, \lambda$
8	17	$1.6692 \cdot 10^2$	$K_{xgI}, K_{xi}, T_{iG}, T_{ghmax}, V_i$
9	17	$1.6873 \cdot 10^2$	$K_{xgI}, T_{iG}, T_{ghmax}, V_g, V_i, \lambda$
10	17	$1.6829 \cdot 10^2$	$K_{xgI}, K_{xi}, T_{iG}, T_{ghmax}, V_g, V_i, \lambda$
RSS represents the Residual Sum of Squares			

Table 5.2: List of Fits (1-10) for Subjects 3, 8 and 17 using the EIC model and the statistical information obtained within FACSMILE i.e. the RSS (Residual Sum of Square) and well determined parameters.

	Fit 1 (Subject 3)		Fit 7 (Subject 8)		Fit 10 (Subject 17)	
Parameters	Value	[SDLN]	Value	[SDLN]	Value	[SDLN]
V_g	$1.223 \cdot 10^{-1}$	[0.957]	$4.034 \cdot 10^{-5}$	[0.692]	$1.568 \cdot 10^{-2}$	[0.555]
V_i	$1.482 \cdot 10^{-1}$	[0.892]	$2.350 \cdot 10^{1}$	[1.400]	$9.073 \cdot 10^{-1}$	[0.427]
K_{xgI}	2.73	[1.002]	$2.385 \cdot 10^{-1}$	[0.789]	$1.820 \cdot 10^{-1}$	[0.849]
K_{xi}	$5.151 \cdot 10^{-2}$	[0.901]	$3.368 \cdot 10^{-2}$	[0.504]	$5.836 \cdot 10^{-2}$	[0.768]
T_{ghmax}	$3.046 \cdot 10^2$	[0.729]	1.549	[1.317]	$2.006 \cdot 10^2$	[0.538]
T_{iG}	$5.827 \cdot 10^2$	[1.110]	6.798	[0.980]	$3.480 \cdot 10^{-1}$	[0.974]
λ	$9.179 \cdot 10^{-3}$	[0.853]	$3.014 \cdot 10^{-2}$	[0.362]	$3.693 \cdot 10^{-2}$	[0.253]
	RSS = $2.2648 \cdot 10^2$		RSS = $3.9811 \cdot 10^2$		RSS = $1.6829 \cdot 10^2$	

Table 5.3: Values and SDLN table of Fits nos. 1 (Subject 3), 7 (Subject 8) and 10 (Subject 17).

	Fit 1 (Subject 3)						
row/column	V_g	K_{xgI}	T_{iG}	K_{xi}	λ	T_{ghmax}	V_i
V_g	1.000	-0.387	-0.427	-0.824	-0.437	- 0.025	0.317
K_{xgI}	-0.387	1.000	-0.338	0.283	-0.518	-0.156	-0.717
T_{iG}	-0.427	-0.338	1.000	0.633	0.349	- 0.378	0.612
K_{xi}	-0.824	0.283	0.633	1.000	0.211	-0.330	-0.222
λ	-0.437	- 0.518	0.349	0.211	1.000	0.628	0.200
T_{ghmax}	-0.025	-0.516	-0.378	-0.330	0.628	1.000	-0.175
V_i	0.317	-0.717	0.612	-0.222	0.200	-0.175	1.000
	Fit 7 (Subject 8)						
row/column	V_g	K_{xgI}	T_{iG}	K_{xi}	λ	T_{ghmax}	V_i
V_g	1.000	-0.174	0.474	-0.514	-0.532	-0.504	0.529
K_{xgI}	-0.174	1.000	0.345	-0.641	-0.667	-0.574	0.458
T_{iG}	0.474	0.345	1.000	-0.734	0.780	-0.893	0.970
K_{xi}	-0.514	-0.641	-0.734	1.000	0.944	0.924	-0.871
λ	-0.532	-0.667	-0.780	0.944	1.000	0.936	-0.887
T_{ghmax}	-0.504	-0.574	-0.893	0.924	0.936	1.000	-0.967
V_i	0.529	0.458	0.970	-0.871	-0.887	-0.967	1.000
	Fit 10 (Subject 17)						
row/column	V_g	K_{xgI}	T_{iG}	K_{xi}	λ	T_{ghmax}	V_i
V_g	1.000	0.148	0.322	0.433	-0.605	-0.483	-0.027
K_{xgI}	0.148	1.000	-0.509	-0.397	-0.792	-0.634	-0.455
T_{iG}	0.322	-0.509	1.000	0.913	0.086	-0.079	0.677
K_{xi}	0.433	-0.397	0.913	1.000	0.015	-0.047	0.322
λ	-0.605	-0.792	0.086	0.015	1.000	0.876	0.174
T_{ghmax}	-0.483	-0.634	-0.079	-0.047	0.876	1.000	-0.114
V_i	-0.027	-0.455	0.677	0.322	0.174	-0.114	1.000

Table 5.4: Correlation Matrix of the well determined parameters for Fit 1 (Subejct 3), Fit 7 (Subject 8) and Fit 10 (Subject 17).

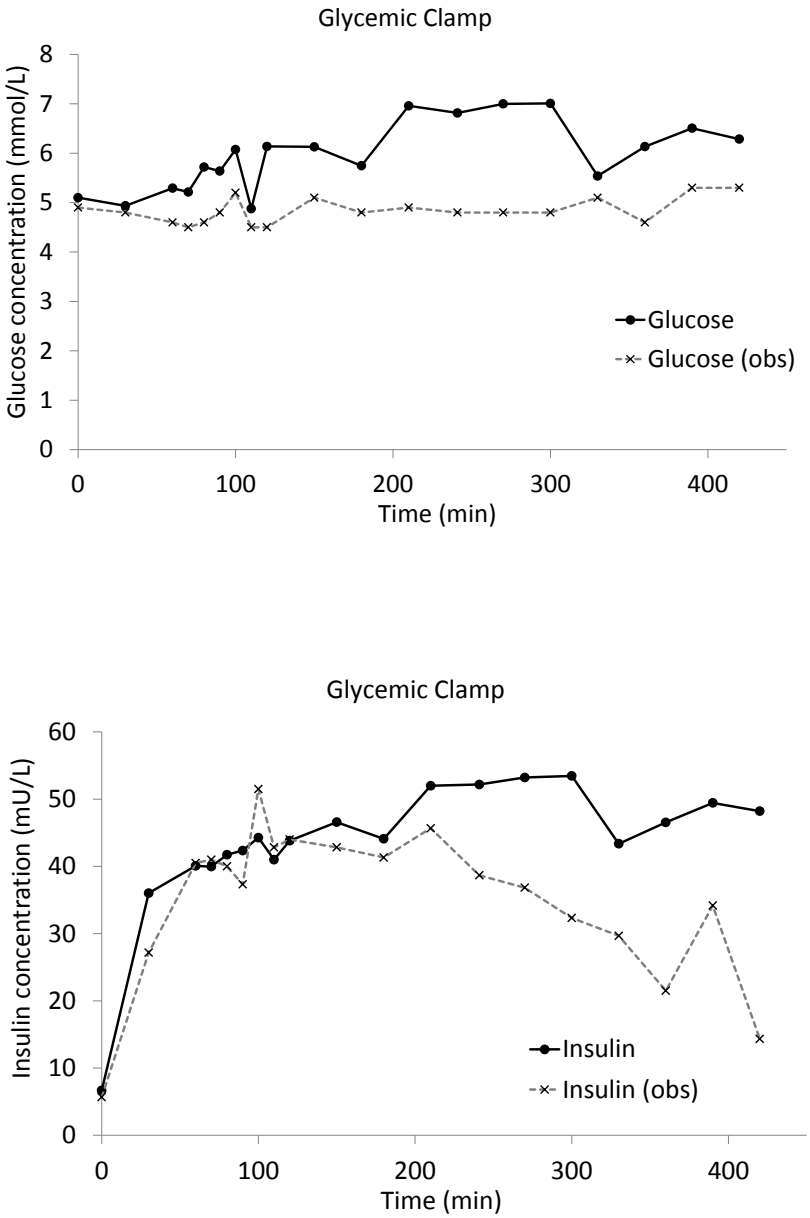

Figure 5.1: Glucose and insulin responses for the EIC model, Fit 1 (Subject 3)

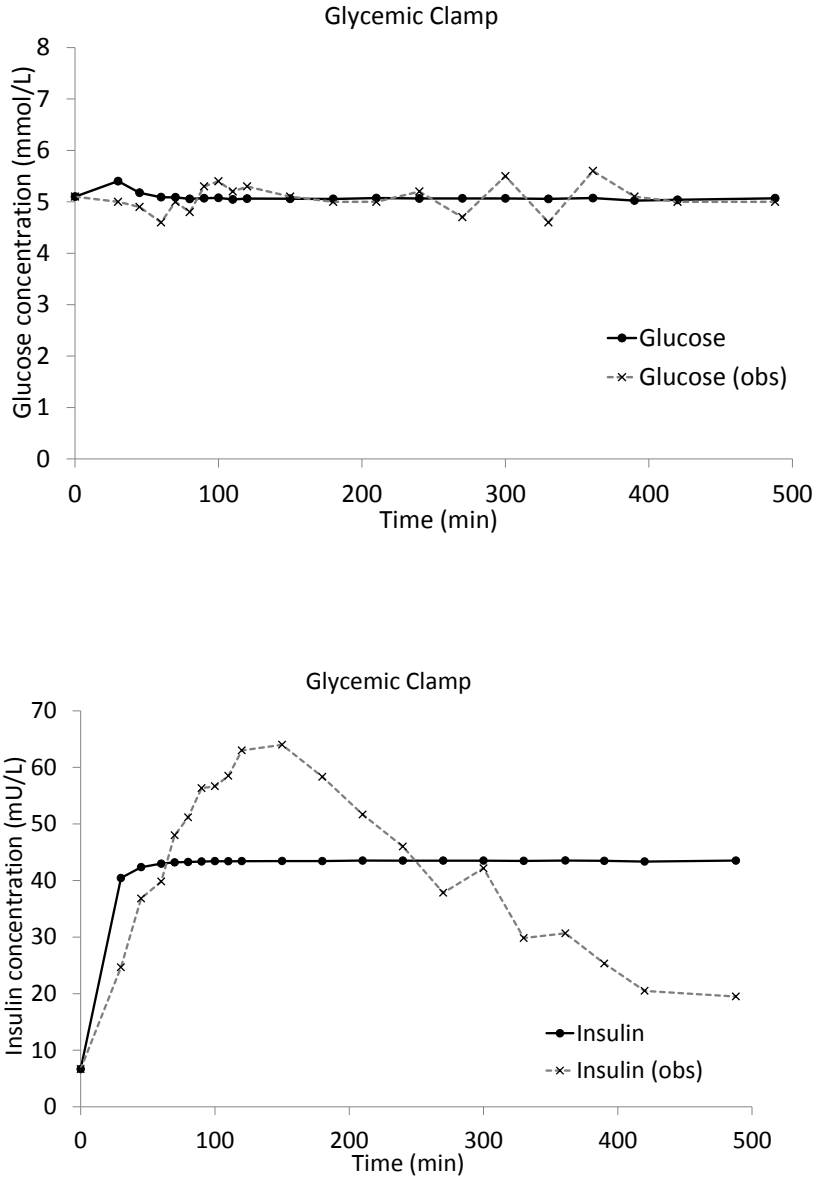

Figure 5.2: Glucose and insulin responses for the EIC model, Fit 7 (Subject 8)

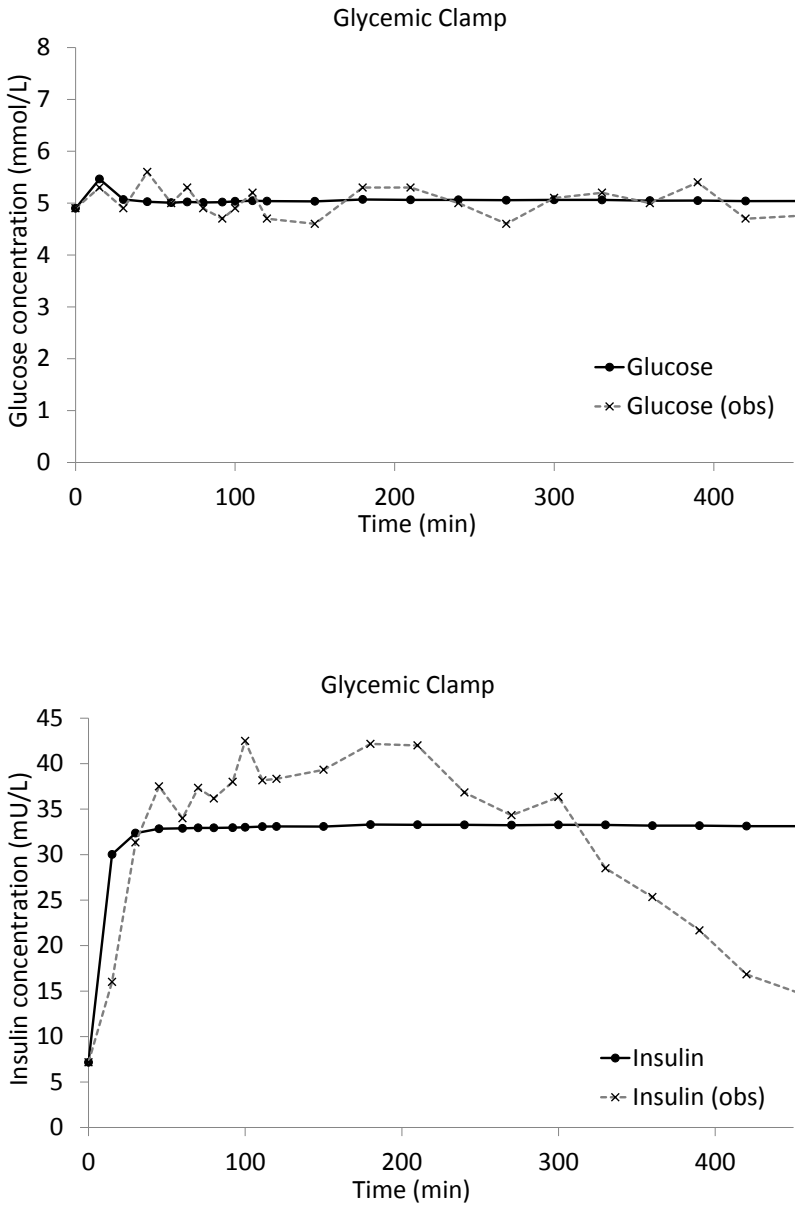

Figure 5.3: Glucose and insulin responses for the EIC model, Fit 10 (Subject 17).

Chapter 6

Structural Identifiability of The Closed-Loop Minimal Model

6.1 Introduction

The Closed-Loop Minimal Model (CLMM) demonstrates the completed glucose-insulin dynamics during the course of an intravenous glucose tolerance test (IVGTT), including the first phase glucose and insulin kinetics, which were not captured in the Extended Minimal Model (EMM). As the model has only recently been introduced by Arundel et al. [2010], as far as the author is aware, a structural identifiability analysis has not yet performed on the CLMM. Therefore, such analysis is essential for any further experimental design or data fitting to be performed using this model. The analysis was performed incorporating a symbolic computational tool, Mathematica [Wolfram, 1996].

The system equations for the CLMM (as shown in Chapter 2 Section

2.6) are given by [Arundel et al., 2010]

$$\begin{aligned}
\dot{G}(t) &= -(p_1 + k_6 I_R(t))G(t) + p_1 G_b, & G(0) &= G_b \\
\dot{I}_R(t) &= k_2(I(t) - I_b) - p_2 I_R(t), & I_R(0) &= 0 \\
\dot{I}(t) &= M_1(G(t) - h)e^{-\lambda t} + \gamma(G(t) - h) - p_{exit} I(t), & I(0) &= I_b
\end{aligned}$$

where $G(t)$ is the glucose concentration; $I(t)$ the insulin concentration and $I_R(t)$ the remote insulin action and the observations of the system are given by

$$y_1(t) = G(t)$$

and

$$y_2(t) = I(t).$$

A structural identifiability of the CLMM was attempted using the Taylor Series approach of [Pohjanpalo, 1978]. However, application of the approach proved difficult due to the complexity of the system structure, and the Taylor Series coefficients generated were too large to make the analysis possible within Mathematica. Therefore, Similarity Transformation approach is considered.

As the model includes a time dependent exponential term and the system is not strictly in the state space form required for application of the Similarity Transformation approach, therefore, a dummy variable is introduced to represent the exponential term. This yields an augmented, but required version of the model in order to perform the analysis using this approach as for the pre-switching phase of the EMM. The dummy variable is given by:

$$W(t) = \exp(-\lambda t)$$

whereby

$$\dot{W}(t) = -\lambda W(t), \qquad W(0) = 1.$$

The augmented version of the CLMM therefore has an additional differential equation to the original state space model and the system equations are given by

$$\dot{G}(t) = -(p_1 + k_6 I_R(t))G(t) + p_1 G_b \tag{6.1}$$

$$\dot{I}_R(t) = k_2(I(t) - I_b) - p_2 I_R(t) \tag{6.2}$$

$$\dot{I}(t) = M_1(G(t) - h)W(t) + \gamma(G(t) - h) - p_{exit} I(t) \tag{6.3}$$

$$\dot{W}(t) = -\lambda W(t). \tag{6.4}$$

The vector of unknown parameters is therefore given by

$$\boldsymbol{p} = (p_1, p_2, p_{exit}, k_2, k_6, M_1, h, \gamma, \lambda, G_b, I_b)^T.$$

6.2 Structural Identifiability Analysis

As the augmented CLMM does not satisfy the Controllability Rank Criterion, it is treated as an autonomous system. Therefore, the Similarity Transformation approach for autonomous systems [Evans et al., 2002] is used for the analysis. Theorem 3.1.5 [Evans et al., 2002] is therefore applied for this analysis.

Consider

$$\mu_1(\boldsymbol{x}, \boldsymbol{p}) = G(t),$$

then choose

$$\begin{aligned}\mu_2(\boldsymbol{x},\boldsymbol{p}) &= L_{fp}\mu_1(\boldsymbol{x}) \\ &= -(p_1 + k_6 I_R(t))G(t) + p_1 G_b.\end{aligned}$$

Then consider

$$\mu_3(\boldsymbol{x},\boldsymbol{p}) = I(t)$$

and choose

$$\begin{aligned}\mu_4(\boldsymbol{x},\boldsymbol{p}) &= L_{fp}\mu_3(\boldsymbol{x}) \\ &= -M_1(G(t)-h)W(t) - \gamma(G(t)-h) - p_{exit}I(t).\end{aligned}$$

Suppose that

$$H(\boldsymbol{x},\boldsymbol{p}) = [\mu_1(\boldsymbol{x},\boldsymbol{p}), \mu_2(\boldsymbol{x},\boldsymbol{p}), \mu_3(\boldsymbol{x},\boldsymbol{p}), \mu_4(\boldsymbol{x},\boldsymbol{p})]^T.$$

Then

$$\frac{\partial H_p(\boldsymbol{x})}{\partial \boldsymbol{x}} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ -(p_1 + k_6 I_R(t)) & k_6 G(t) & 0 & 0 \\ 0 & 0 & 1 & 0 \\ \gamma + M_1 W(t) & 0 & -p_{exit} & M_1(G(t)-h) \end{bmatrix}$$

which has rank 4, i.e. has full rank. Hence the ORC is satisfied.

Eqn. (3.21) is given by

$$\boldsymbol{f}(\lambda(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),\boldsymbol{p}) = \begin{bmatrix} \frac{\partial\lambda_1}{\partial G} & \frac{\partial\lambda_1}{\partial I_R} & \frac{\partial\lambda_1}{\partial I} & \frac{\partial\lambda_1}{\partial W} \\ \frac{\partial\lambda_2}{\partial G} & \frac{\partial\lambda_2}{\partial I_R} & \frac{\partial\lambda_2}{\partial I} & \frac{\partial\lambda_2}{\partial W} \\ \frac{\partial\lambda_3}{\partial G} & \frac{\partial\lambda_3}{\partial I_R} & \frac{\partial\lambda_3}{\partial I} & \frac{\partial\lambda_3}{\partial W} \\ \frac{\partial\lambda_4}{\partial G} & \frac{\partial\lambda_4}{\partial I_R} & \frac{\partial\lambda_4}{\partial I} & \frac{\partial\lambda_4}{\partial W} \end{bmatrix} \boldsymbol{f}(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}). \tag{6.5}$$

The system observations, Eqn. (3.19) give the following

$$\begin{bmatrix} 1 & 0 & 1 & 0 \end{bmatrix} \begin{bmatrix} \lambda_1(\boldsymbol{x}) \\ \lambda_2(\boldsymbol{x}) \\ \lambda_3(\boldsymbol{x}) \\ \lambda_4(\boldsymbol{x}) \end{bmatrix} = \begin{bmatrix} 1 & 0 & 1 & 0 \end{bmatrix} \begin{bmatrix} G \\ I_R \\ I \\ W \end{bmatrix}.$$

whereby

$$\lambda_1(\boldsymbol{x}) = G$$

and

$$\lambda_3(\boldsymbol{x}) = I,$$

Therefore,

$$\frac{\partial\lambda_1(\boldsymbol{x})}{\partial G} = 1 \tag{6.6}$$

$$\frac{\partial\lambda_1(\boldsymbol{x})}{\partial I_R} = \frac{\partial\lambda_1(\boldsymbol{x})}{\partial I} = \frac{\partial\lambda_1(\boldsymbol{x})}{\partial W} = 0 \tag{6.7}$$

and

$$\frac{\partial\lambda_3(\boldsymbol{x})}{\partial I} = 1 \tag{6.8}$$

$$\frac{\partial\lambda_3(\boldsymbol{x})}{\partial G} = \frac{\partial\lambda_3(\boldsymbol{x})}{\partial I_R} = \frac{\partial\lambda_3(\boldsymbol{x})}{\partial W} = 0. \tag{6.9}$$

Substituting Eqns. (6.6) - (6.9) into Eqn. (6.5) gives

$$\boldsymbol{f}(\lambda(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),\boldsymbol{p}) = \begin{bmatrix} 1 & 0 & 0 & 0 \\ \frac{\partial\lambda_2}{\partial G} & \frac{\partial\lambda_2}{\partial I_R} & \frac{\partial\lambda_2}{\partial I} & \frac{\partial\lambda_2}{\partial W} \\ 0 & 0 & 1 & 0 \\ \frac{\partial\lambda_4}{\partial G} & \frac{\partial\lambda_4}{\partial I_R} & \frac{\partial\lambda_4}{\partial I} & \frac{\partial\lambda_4}{\partial W} \end{bmatrix} \boldsymbol{f}(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}). \tag{6.10}$$

The first component of Eqn. (6.10) is given by

$$\begin{aligned} \boldsymbol{f}_1(\lambda(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),\boldsymbol{p}) &= \mu_2(\lambda(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),\boldsymbol{p}) \\ &= \boldsymbol{f}_1(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}},\bar{\boldsymbol{p}}) = \mu_2(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) \end{aligned}$$

and hence

$$-(p_1 + k_6\lambda_2(\boldsymbol{x}))G + p_1G_b = -(\bar{p} + \bar{k}_6I_R)G + \bar{p}_1\bar{G}_b \tag{6.11}$$

which after rearranging yields

$$\lambda_2(\boldsymbol{x}) = \frac{GI_R\bar{k}_6 - Gp_1 + G_bp_1 - \bar{G}_b\bar{p}_1 + G\bar{p}_1}{Gk_6}$$

and so

$$\frac{\partial\lambda_2(\boldsymbol{x})}{\partial G} = \frac{-G_bp_1 + \bar{G}_b\bar{p}_1}{G^2k_6},$$

$$\frac{\partial\lambda_2(\boldsymbol{x})}{\partial I_R} = \frac{\bar{k}_6}{k_6},$$

and

$$\frac{\partial\lambda_2(\boldsymbol{x})}{\partial I} = \frac{\partial\lambda_2(\boldsymbol{x})}{\partial W} = 0.$$

The second component of Eqn. (6.10) is satisfied if and only if

$$\boldsymbol{f}_3(\lambda(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),\boldsymbol{p}) - \frac{\partial\lambda_2}{\partial G}\boldsymbol{f}_1(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) - \frac{\partial\lambda_2}{\partial I_R}\boldsymbol{f}_2(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) = 0 \tag{6.12}$$

whereby

$$k_2(I-I_b) - p_2\lambda_2(\boldsymbol{x}) - \left(\frac{-G_b p_1 + \bar{G}_b\bar{p}_1}{G^2 k_6}\right)(-(\bar{p}_1 + \bar{k}_6 I_R)G + \bar{p}_1\bar{G}_b) \\ - \left(\frac{\bar{k}_6}{k_6}\right)(\bar{k}_2(I-\bar{I}_b) - \bar{p}_2 I_R) = 0$$

and

$$-G\big((G_b p_1 - \bar{G}_b\bar{p}_1)p_2 + G(I_b k_2 k_6 + I_R\bar{k}_6 p_2 - p_1 p_2 + \bar{p}_1 p_2 - k_2 k_6 I)\big) \\ -G(I_R\bar{k}_6 + \bar{p}_1)(G_b p_1 - \bar{G}_b\bar{p}_1) - \bar{G}_b\bar{p}_1(-G_b p_1 + \bar{G}_b\bar{p}_1) \\ +G^2\bar{k}_6(\bar{I}_b\bar{k}_2 + I_R\bar{p}_2 - \bar{k}_2 I) = 0$$

which satify Eqn. (6.12) as

$$q_1(\boldsymbol{p},\bar{\boldsymbol{p}})G^2(t,\bar{\boldsymbol{p}}) + q_2(\boldsymbol{p},\bar{\boldsymbol{p}})G^2(t,\bar{\boldsymbol{p}})I_R(t,\bar{\boldsymbol{p}}) + q_3(\boldsymbol{p},\bar{\boldsymbol{p}})G^2(t,\bar{\boldsymbol{p}})I(t,\bar{\boldsymbol{p}}) \\ +q_4(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}})I_R(t,\bar{\boldsymbol{p}}) + q_5(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}}) + q_6(\boldsymbol{p},\bar{\boldsymbol{p}}) = 0$$

where

$$\begin{aligned}
q_1(\boldsymbol{p},\bar{\boldsymbol{p}}) &= -I_b k_2 k_6 + \bar{I}_b\bar{k}_2\bar{k}_6 + p_1 p_2 - \bar{p}_1 p_2 \\
q_2(\boldsymbol{p},\bar{\boldsymbol{p}}) &= -\bar{k}_6 p_2 + \bar{k}_6\bar{p}_2 \\
q_3(\boldsymbol{p},\bar{\boldsymbol{p}}) &= -\bar{k}_2\bar{k}_6 + k_2 k_6 \\
q_4(\boldsymbol{p},\bar{\boldsymbol{p}}) &= -G_b\bar{k}_6 p_1 + \bar{G}_b\bar{k}_6\bar{p}_1 \\
q_5(\boldsymbol{p},\bar{\boldsymbol{p}}) &= -G_b p_1\bar{p}_1 + \bar{G}_b\bar{p}_1^2 - G_b p_1 p_2 + \bar{G}_b\bar{p}_1 p_2 \\
q_6(\boldsymbol{p},\bar{\boldsymbol{p}}) &= -\bar{G}_b^2\bar{p}_1^2 + G_b\bar{G}_b p_1\bar{p}_1.
\end{aligned}$$

This polynomial must be identically zero. Therefore each of its coefficients

must be zero for all ($t \in [0, \tau)$) hence

$$q_1(\boldsymbol{p}, \bar{\boldsymbol{p}}) = q_2(\boldsymbol{p}, \bar{\boldsymbol{p}}) = q_3(\boldsymbol{p}, \bar{\boldsymbol{p}}) = q_4(\boldsymbol{p}, \bar{\boldsymbol{p}}) = q_5(\boldsymbol{p}, \bar{\boldsymbol{p}}) = q_6(\boldsymbol{p}, \bar{\boldsymbol{p}}) = 0.$$

Solving this system of algebraic equations, it can be concluded that

$$p_2 = \bar{p}_2 \tag{6.13}$$

$$k_2 k_6 = \bar{k}_2 \bar{k}_6 \tag{6.14}$$

$$G_b p_1 = \bar{G}_b \bar{p}_1 \tag{6.15}$$

and

$$-\bar{I}_b \bar{k}_2 \bar{k}_6 + I_b k_2 k_6 = p_1 p_2 - \bar{p}_1 p_2 \tag{6.16}$$

and substituting $k_2 k_6 = \bar{k}_2 \bar{k}_6$ and $p_2 = \bar{p}_2$ into Eqn. (6.16) gives

$$\bar{k}_2 \bar{k}_6 (\bar{I}_b - I_b) = p_2 (\bar{p}_1 - p_1). \tag{6.17}$$

The third component of Eqn. (6.10) gives

$$\begin{aligned} \boldsymbol{f}_3(\lambda(\boldsymbol{x}(t, \bar{\boldsymbol{p}})), \boldsymbol{p}) &= \mu_4(\lambda(\boldsymbol{x}(t, \bar{\boldsymbol{p}})), \bar{\boldsymbol{p}}) \\ &= \boldsymbol{f}_3(\boldsymbol{x}(t, \bar{\boldsymbol{p}})), \bar{\boldsymbol{p}}) = \mu_4(\boldsymbol{x}(t, \bar{\boldsymbol{p}}), \bar{\boldsymbol{p}}) \end{aligned}$$

which gives

$$\begin{aligned} M_1(\lambda_1(\boldsymbol{x}) - h)\lambda_4(\boldsymbol{x}) + \gamma(\lambda_1(\boldsymbol{x}) - h) - p_{exit}\lambda_3(\boldsymbol{x}) - \bar{M}_1(G - \bar{h})W \\ -\bar{\gamma}(G - \bar{h}) + \bar{p}_{exit} I = 0 \end{aligned}$$

and after arranging this yields

$$\lambda_4(\boldsymbol{x}) = \frac{G(-\gamma+\bar{\gamma}) + \gamma h - \bar{\gamma}\bar{h} + I(p_{exit} - \bar{p}_{exit}) + W(G\bar{M}_1 - \bar{h}\bar{M}_1)}{(G-h)M_1}$$

whereby

$$\frac{\partial \lambda_4(\boldsymbol{x})}{\partial G} = \frac{\bar{\gamma}(-h+\bar{h}) - p_{exit}I + \bar{p}_{exit} - h\bar{M}_1 W + \bar{h}\bar{M}_1 W}{(G-h)^2 M_1},$$

$$\frac{\partial \lambda_4(\boldsymbol{x})}{\partial I_R} = 0,$$

$$\frac{\partial \lambda_4(\boldsymbol{x})}{\partial I} = \frac{p_{exit} - \bar{p}_{exit}}{(G-h)M_1},$$

and

$$\frac{\partial \lambda_4(\boldsymbol{x})}{\partial W} = \frac{(G-\bar{h})\bar{M}_1}{(G-h)M_1}.$$

The fourth component of Eqn. (6.10) is satisfied if and only if

$$\begin{aligned}\boldsymbol{f}_4(\lambda(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\boldsymbol{p}) - \frac{\partial \lambda_4(\boldsymbol{x})}{\partial G}\boldsymbol{f}_1(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) - \frac{\partial \lambda_4(\boldsymbol{x})}{\partial I}\boldsymbol{f}_3(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) \\ - \frac{\partial \lambda_4(\boldsymbol{x})}{\partial W}\boldsymbol{f}_4(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) = 0.\end{aligned} \tag{6.18}$$

Therefore,

$$\begin{aligned}&-(G-h)\lambda(-G\gamma + G\bar{\gamma} - \gamma h - \bar{\gamma}\bar{h} - \bar{p}_{exit}I + G\bar{M}_1 W - \bar{h}\bar{M}_1 W) \\ &-(G-h)(-G+\bar{h})\bar{\lambda}\bar{M}_1 W - (-\bar{G}_b\bar{p}_1 + G(I_R\bar{k}_6 + \bar{p}_1))(\bar{\gamma}(h-\bar{h}) \\ &+p_{exit}I - \bar{p}_{exit}I + h\bar{M}_1 W - \bar{h}\bar{M}_1 W) + (G-h)(p_{exit} - \bar{p}_{exit})(\bar{\gamma}\bar{h} \\ &+p_{exit}I + \bar{h}\bar{M}_1 W - G(\bar{\gamma} + \bar{M}_1 W)) = 0\end{aligned}$$

which satisfy Eqn. (6.18) given by

$$\begin{aligned}
&c_1(\boldsymbol{p},\bar{\boldsymbol{p}})G^2(t,\bar{\boldsymbol{p}}) + c_2(\boldsymbol{p},\bar{\boldsymbol{p}})G^2(t,\bar{\boldsymbol{p}})W(t,\bar{\boldsymbol{p}}) + c_3(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}}) \\
&+c_4(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}})I_R(t,\bar{\boldsymbol{p}}) + c_5(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}})I_R(t,\bar{\boldsymbol{p}})I(t,\bar{\boldsymbol{p}}) \\
&+c_6(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}})I(t,\bar{\boldsymbol{p}}) + c_7(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}})I_R(t,\bar{\boldsymbol{p}})W(t,\bar{\boldsymbol{p}}) + c_{11}(\boldsymbol{p},\bar{\boldsymbol{p}}) \\
&+c_8(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}})W(t,\bar{\boldsymbol{p}}) + c_9(\boldsymbol{p},\bar{\boldsymbol{p}})I(t,\bar{\boldsymbol{p}}) + c_{10}(\boldsymbol{p},\bar{\boldsymbol{p}})W(t,\bar{\boldsymbol{p}}) = 0
\end{aligned}$$

where

$$\begin{aligned}
c_1(\boldsymbol{p},\bar{\boldsymbol{p}}) = \;& \gamma\lambda - \bar{\gamma}\bar{\lambda} - \bar{\gamma}p_{exit} + \bar{\gamma}\bar{p}_{exit} \\
c_2(\boldsymbol{p},\bar{\boldsymbol{p}}) = \;& -\lambda\bar{M}_1 + \bar{\lambda}\bar{M}_1 - \bar{M}_1 p_{exit} + \bar{M}\bar{p}_{exit} \\
c_3(\boldsymbol{p},\bar{\boldsymbol{p}}) = \;& -2\gamma h\lambda + \bar{\gamma}h\lambda + \bar{\gamma}\bar{h}\lambda - \bar{\gamma}h\bar{p}_1 + \bar{\gamma}\bar{h}\bar{p}_1 + \bar{\gamma}hp_{exit} + \bar{\gamma}\bar{h}p_{exit} \\
& +I_b\lambda p_{exit} + I_b\bar{p}_1 p_{exit} - \bar{\gamma}h\bar{p}_{exit} - \bar{\gamma}\bar{h}\bar{p}_{exit} - \bar{I}_b\lambda\bar{p}_{exit} \\
& -\bar{I}_b\bar{p}_1\bar{p}_{exit} - \bar{I}_b p_{exit}\bar{p}_{exit} + \bar{I}_b\bar{p}_{exit}^2 \\
c_4(\boldsymbol{p},\bar{\boldsymbol{p}}) = \;& -\bar{\gamma}h\bar{k}_6 + \bar{\gamma}\bar{h}\bar{k}_6 - \bar{I}_b\bar{k}_6\bar{p}_{exit} + I_b\bar{k}_6 p_{exit} \\
c_5(\boldsymbol{p},\bar{\boldsymbol{p}}) = \;& -\bar{k}_6 p_{exit} + \bar{k}_6\bar{p}_{exit} \\
c_6(\boldsymbol{p},\bar{\boldsymbol{p}}) = \;& -\lambda p_{exit} - \bar{p}_1 p_{exit} + \lambda\bar{p}_{exit} + \bar{p}_1\bar{p}_{exit} + p_{exit}\bar{p}_{exit} - \bar{p}_{exit}^2 \\
c_7(\boldsymbol{p},\bar{\boldsymbol{p}}) = \;& -h\bar{k}_6\bar{M}_1 + \bar{h}\bar{k}_6\bar{M}_1 \\
c_8(\boldsymbol{p},\bar{\boldsymbol{p}}) = \;& h\lambda\bar{M}_1 + \bar{h}\lambda\bar{M}_1 - h\bar{\lambda}\bar{M}_1 - \bar{h}\bar{\lambda}\bar{M}_1 - h\bar{M}_1\bar{p}_1 + \bar{h}\bar{M}_1\bar{p}_1 \\
& +h\bar{M}_1 p_{exit} + \bar{h}\bar{M}_1 p_{exit} - h\bar{M}_1\bar{p}_{exit} - \bar{h}\bar{M}_1\bar{p}_{exit} \\
c_9(\boldsymbol{p},\bar{\boldsymbol{p}}) = \;& h\lambda p_{exit} + \bar{G}_b\bar{p}_1 p_{exit} - h\lambda\bar{p}_{exit} - \bar{G}_b\bar{p}_1\bar{p}_{exit} - hp_{exit}\bar{p}_{exit} \\
& +h\bar{p}_{exit}^2 \\
c_{10}(\boldsymbol{p},\bar{\boldsymbol{p}}) = \;& -h\bar{h}\lambda\bar{M}_1 + h\bar{h}\bar{\lambda}\bar{M}_1 + \bar{G}_b h\bar{M}_1\bar{p}_1 - \bar{G}_b\bar{h}\bar{M}_1\bar{p}_1 - h\bar{h}\bar{M}_1 p_{exit} \\
& +h\bar{h}\bar{M}_1\bar{p}_{exit} \\
c_{11}(\boldsymbol{p},\bar{\boldsymbol{p}}) = \;& \gamma h^2\lambda - \bar{\gamma}h\bar{h}\lambda + \bar{\gamma}\bar{G}_b h\bar{p}_1 - \bar{\gamma}\bar{G}_b\bar{h}\bar{p}_1 - \bar{\gamma}h\bar{h}p_{exit} \\
& -\bar{G}_b I_b\bar{p}_1 p_{exit} + \bar{\gamma}h\bar{h}\bar{p}_{exit} + h\bar{I}_b\lambda\bar{p}_{exit} + \bar{G}_b\bar{I}_b\bar{p}_1\bar{p}_{exit} \\
& +h\bar{I}_b p_{exit}\bar{p}_{exit} - h\bar{I}_b\bar{p}_{exit}^2 - hI_b\lambda p_{exit}.
\end{aligned}$$

The polynomial must be identically zero. Therefore each of its coefficients must be zero ($t \in [0, \tau)$), hence

$$\begin{aligned} c_1(\boldsymbol{p}, \bar{\boldsymbol{p}}) = c_2(\boldsymbol{p}, \bar{\boldsymbol{p}}) = c_3(\boldsymbol{p}, \bar{\boldsymbol{p}}) = c_4(\boldsymbol{p}, \bar{\boldsymbol{p}}) = c_5(\boldsymbol{p}, \bar{\boldsymbol{p}}) = c_6(\boldsymbol{p}, \bar{\boldsymbol{p}}) \\ = c_7(\boldsymbol{p}, \bar{\boldsymbol{p}}) = c_8(\boldsymbol{p}, \bar{\boldsymbol{p}}) = c_9(\boldsymbol{p}, \bar{\boldsymbol{p}}) = c_{10}(\boldsymbol{p}, \bar{\boldsymbol{p}}) = c_{11}(\boldsymbol{p}, \bar{\boldsymbol{p}}) = 0. \end{aligned}$$

Solving this system of algebraic equations, it can be concluded that

$$h = \bar{h} \tag{6.19}$$

$$p_{exit} = \bar{p}_{exit} \tag{6.20}$$

$$-\lambda + \bar{\lambda} = p_{exit} - \bar{p}_{exit} \tag{6.21}$$

$$\gamma = \bar{\gamma} \tag{6.22}$$

$$\gamma\lambda - \bar{\lambda}\bar{\gamma} = \bar{\gamma}p_{exit} - \bar{\gamma}\bar{p}_{exit}. \tag{6.23}$$

Substituting Eqn. (6.20) into Eqn. (6.21) gives

$$\lambda = \bar{\lambda}. \tag{6.24}$$

Substituting Eqn. (6.20) and (6.24) into (6.23) gives

$$\gamma = \bar{\gamma}. \tag{6.25}$$

In conclusion, the outcome for the parameters from the structural identifiability analysis is given by

$$p_1 G_b = \bar{p}_1 \bar{G}_b$$

$$p_2 = \bar{p}_2$$

$$p_{exit} = \bar{p}_{exit}$$

$$k_2 k_6 = \bar{k}_2 \bar{k}_6$$

$$h = \bar{h}$$

$$\lambda = \bar{\lambda}$$

$$\gamma = \bar{\gamma}$$

$$I_b = -\frac{p_2(\bar{p}_1 - p_1)}{\bar{k}_2 \bar{k}_6} + \bar{I}_b.$$

Therefore, the parameters $p_2 = \bar{p}_2$, $h = \bar{h}$, $p_{exit} = \bar{p}_{exit}$, $\lambda = \bar{\lambda}$, $\gamma = \bar{\gamma}$ are uniquely identifiable without any constraints. Under the condition that the parameter G_b is known (or measurable in the real system), then the parameters p_1 and I_b are also uniquely identifiable.

The parameters k_2 and k_6 are unidentifiable as these two parameters appear only as a product thoughout. The parameter M_1 is also unidentifiable, as no further information can be obtained for it. Therefore, the system is structurally unidentifiable for this experiment.

The CLMM in this form is structurally unidentifiable, therefore further information is needed for the system parameters or a reparameterisation process can be carried out in order to yield a model that is at least locally identifiable, but with a reduced set of parameters.

6.3 Reparameterisation

The structural identifiability analysis using a version of Similarity Transformation Approach by Evans et al. [2005] (in section 6.2) shows that the augmented version of the CLMM is structurally unidentifiable. Therefore, a reparameterisation process is considered. The system equations for the CLMM Eqns. (6.1)

- (6.4) are given by

$$\begin{aligned}
\dot{G}(t) &= -(p_1 + k_6 I_R(t))G(t) + p_1 G_b \\
\dot{I}_R(t) &= k_2(I(t) - I_b) - p_2 I_R(t) \\
\dot{I}(t) &= M_1(G(t) - h)W(t) + \gamma(G(t) - h) - p_{exit} I(t) \\
\dot{W}(t) &= -\lambda W(t)
\end{aligned}$$

where the observations are given by

$$y_1(t) = G(t)$$

and

$$y_2(t) = I(t).$$

Applying Theorem 3.1.5, the first component of Eqn. (3.21) gives

$$-(p_1 + k_6\lambda_2)G + p_1 G_b = -(\bar{p}_1 + \bar{k}_6 I_R)G + \bar{p}_1 \bar{G}_b. \tag{6.26}$$

After rearranging, Eqn. (6.26) this gives

$$\lambda_2 = \frac{G I_R \bar{k}_6 - G p_1 + G_b p_1 - \bar{G}_b \bar{p}_1 + G\bar{p}_1}{G k_6}. \tag{6.27}$$

Substituting $p_2 = \bar{p}_2$ and $G_b p_1 = \bar{G}_b \bar{p}_1$ from (6.13) and (6.15) respectively, the second component of Eqn. (3.21) gives

$$G^2(-I_b k_2 k_6 + \bar{I}_b \bar{k}_2 \bar{k}_6 - p_1 p_2 - \bar{p}_1 p_2 + k_2 k_6 I - \bar{k}_2 \bar{k}_6 I) = 0. \tag{6.28}$$

Expanding Eqn. (6.28) as a Taylor Series in $G(t)$ around $G(0) = G_b$ and $I(t)$

around $I(0) = I_b$ give

$$\begin{aligned} -G_b^2 I_b \bar{k}_2 \bar{k}_6 + G_b^2 \bar{I}_b \bar{k}_2 \bar{k}_6 + G_b^2 p_1 \bar{p}_2 - G_b^2 \bar{p}_1 \bar{p}_2 \\ +(G_b^2 k_2 k_6 - G_b^2 \bar{k}_2 \bar{k}_6)(I - I_b) \\ +(-2G_b I_b \bar{k}_2 \bar{k}_6 + 2G_b \bar{I}_b \bar{k}_2 \bar{k}_6 + 2G_b p_1 \bar{p}_2 - 2G_b \bar{p}_1 \bar{p}_2)(G - G_b) \\ +(2G_b k_2 k_6 - 2G_b \bar{k}_2 \bar{k}_6)(I - I_b)(G - G_b) \\ +(-I_b \bar{k}_2 \bar{k}_6 + \bar{I}_b \bar{k}_2 \bar{k}_6 + p_1 \bar{p}_2 - \bar{p}_1 \bar{p}_2)(G - G_b)^2 \\ +(k_2 k_6 - \bar{k}_2 \bar{k}_6)(I - I_b)(G - G_b)^2 = 0 \end{aligned} \tag{6.29}$$

which yields the sequence of coefficients $F_1^{(i)}(p)$, $i = 1, 2, ...$, as

$$F_1^{(1)}(\boldsymbol{p}) = -I_b k_2 k_6 + \bar{I}_b \bar{k}_2 \bar{k}_6 + p_1 \bar{p}_2 - \bar{p}_1 \bar{p}_2 = 0 \tag{6.30}$$

$$F_1^{(2)}(\boldsymbol{p}) = k_2 k_6 - \bar{k}_2 \bar{k}_6 = 0 \tag{6.31}$$

$$\vdots \qquad\qquad \vdots$$

Consider the partial derivates of the coefficients $F_1^{(1)}$, $F_1^{(2)}$ with respect to $\boldsymbol{p} = (k_2, k_6)$, the infinite jacobian matrix $J(\boldsymbol{p})$ can be generated to give

$$J(\boldsymbol{p}) = \begin{bmatrix} -I_b k_6 & -I_b k_2 \\ k_6 & k_2 \\ \vdots & \vdots \end{bmatrix} \tag{6.32}$$

which has rank 1. This matrix $J(\boldsymbol{p})$ is rank deficient by one. According to Theorem 3.2.1 implies that there is one redundant parameter and a reparameterisation of the system consisting only 10 parameters,

$$\boldsymbol{\phi} = (\phi_1, \phi_2, \phi_3, \phi_4, \phi_5, \phi_6, \phi_7, \phi_8, \phi_9, \phi_{10}) \tag{6.33}$$

instead of 11 parameters in the original model. The one-dimensional null space

of (6.32) is spanned by the vector

$$-\frac{k_2}{k_6}\frac{\partial \boldsymbol{\phi}(\boldsymbol{p})}{\partial k_2} + \frac{\partial \boldsymbol{\phi}(\boldsymbol{p})}{\partial k_6} = 0 \tag{6.34}$$

whereby

$$n = \left(-\frac{k_2}{k_6}, 1\right). \tag{6.35}$$

The structural identifiability analysis in Section 6.2 shows that the parameter M_1 was effectively eliminated from the analysis and its identifiability cannot be determined from the system, therefore, one obvious consideration is to eliminate the parameter M_1 from the reparameterised system. Therefore, the total number of parameters is reduced further and is given by

$$\boldsymbol{\phi} = (\phi_1, \phi_2, \phi_3, \phi_4, \phi_5, \phi_6, \phi_7, \phi_8, \phi_9). \tag{6.36}$$

To solve for the function $\boldsymbol{\phi}$ of Theorem 3.2.1, where $\boldsymbol{\phi}(\boldsymbol{p})$ provides locally identifiable combinations of the original parameters, we consider the orthogonality condition (3.36) whereby

$$\left(-\frac{k_2}{k_6}, 1\right) \cdot \left(\frac{\partial \boldsymbol{\phi}(\boldsymbol{p})}{\partial k_2}, \frac{\partial \boldsymbol{\phi}(\boldsymbol{p})}{\partial k_6}\right) = 0 \tag{6.37}$$

or

$$-\frac{k_2}{k_6}\frac{\partial \boldsymbol{\phi}(\boldsymbol{p})}{\partial k_2} + \frac{\partial \boldsymbol{\phi}(\boldsymbol{p})}{\partial k_6} = 0 \tag{6.38}$$

one of the possible solutions for Eqn. (6.38) are given by

$$\begin{aligned} \boldsymbol{\phi}(\boldsymbol{p}) &= k_2 k_6 \\ &\vdots \end{aligned} \tag{6.39}$$

These possible solutions, i.e. the term on the right-hand sides of Eqn.

(6.39) is locally identifiable parameter combinations for the tested system (6.1) - (6.4). The system (6.1) - (6.4) may therefore be rearranged with a reduced set of parameters (9 parameters) through groupings of the original parameter, consider the following transformation

$$I_R = I_R^* k_2$$

and

$$W = \frac{W^*}{M_1}$$

which, when substituted into the system equations (6.1) - (6.4) give

$$\begin{aligned}
\dot{G}(t) &= -\big(p_1 + k_6 k_2 I_R^*(t)\big)G(t) + p_1 G_b \\
\dot{I}_R^*(t)k_2 &= k_2\big(I(t) - I_b\big) - p_2 k_2 I_R^*(t) \\
\dot{I}(t) &= \big(G(t) - h\big)W^*(t) + \gamma\big(G(t) - h\big) - p_{exit} I(t) \\
\dot{W^*}(t) &= -\lambda W^*(t)
\end{aligned}$$

which after rearranging gives

$$\begin{aligned}
\dot{G}(t) &= -\big(p_1 + k_2 k_6 I_R^*(t)\big)G(t) - p_1 G_b \\
\dot{I}_R^*(t) &= I(t) - I_b - p_2 I_R^*(t) \\
\dot{I}(t) &= \big(G(t) - h\big)W^*(t) + \gamma\big(G(t) - h\big) - p_{exit} I(t) \\
\dot{W}^*(t) &= -\lambda W^*(t).
\end{aligned}$$

The reparameterised, at least locally identifiable, system of the augmented

CLMM is then given by

$$\dot{G}(t) = -\big(\phi_1 + \phi_2 I_R^*(t)\big)G(t) + \phi_1\phi_3 \tag{6.40}$$

$$\dot{I}_R^*(t) = I(t) - \phi_4 - \phi_5 I_R^*(t) \tag{6.41}$$

$$\dot{I}(t) = \big(G(t) - \phi_6\big)W^*(t) + \phi_7\big(G(t) - \phi_6\big) - \phi_8 I(t) \tag{6.42}$$

$$\dot{W}^*(t) = -\phi_9 W^*(t). \tag{6.43}$$

The reparameterised model is now given by

$$\dot{G}(t) = -\big(\phi_1 + \phi_2 I_R^*(t)\big)G(t) + \phi_1\phi_3 \tag{6.44}$$

$$\dot{I}_R^*(t) = I(t) - \phi_4 - \phi_5 I_R^*(t) \tag{6.45}$$

$$\dot{I}(t) = \big(G(t) - \phi_6\big)\exp(-\phi_9 t) + \phi_7\big(G(t) - \phi_6\big) - \phi_8 I(t) \tag{6.46}$$

and the initial conditions are given by

$$\dot{G}(0) = G_b$$

$$\dot{I}_R^*(0) = 0$$

and

$$\dot{I}(0) = I_b$$

with the new locally identifiable parameter set ϕ_1, ϕ_2, ϕ_3, ϕ_4, ϕ_5, ϕ_6, ϕ_7, ϕ_8, ϕ_9.

6.4 Structural Identifiability of the Reparameterised Closed-Loop Minimal Model

As the reparameterised model still consists of a time dependent exponential term, the augmented version of the model is considered, i.e. Eqns. (6.40) - (6.43) and are given by

$$\begin{aligned}
\dot{G}(t) &= -(\phi_1 + \phi_2 I_R^*(t))G(t) + \phi_1\phi_3 \\
\dot{I}_R^*(t) &= I(t) - \phi_4 - \phi_5 I_R^*(t) \\
\dot{I}(t) &= (G(t) - \phi_6)W^*(t) + \phi_7(G(t) - \phi_6) - \phi_8 I(t) \\
\dot{W}^*(t) &= -\phi_9 W^*(t)
\end{aligned}$$

and the new unknown parameter vector is

$$\boldsymbol{p} = [\phi_1, \phi_2, \phi_3, \phi_4, \phi_5, \phi_6, \phi_7, \phi_8, \phi_9]^T.$$

The observations of the system are given by

$$y_1(t) = G(t)$$

and

$$y_2(t) = I(t).$$

A structural identifiability analysis is performed on the reparameterised CLMM by applying the same method as for the original form of the model, i.e. the Similarity Transformation approach for autonomous systems [Evans et al., 2002]. Theorem 3.1.5 is then again applied.

Consider

$$\mu_1(\boldsymbol{x}, \boldsymbol{p}) = G(t)$$

then choose

$$\begin{aligned}\mu_2(\boldsymbol{x},\boldsymbol{p}) &= L_{fp}\mu_1(\boldsymbol{x}) \\ &= -(\phi_1+\phi_2 I_R^*(t))G(t)+\phi_1\phi_3.\end{aligned}$$

Consider now

$$\mu_3(\boldsymbol{x},\boldsymbol{p}) = I(t)$$

then choose

$$\begin{aligned}\mu_4(\boldsymbol{x},\boldsymbol{p}) &= L_{fp}\mu_3(\boldsymbol{x}) \\ &= (G(t)-\phi_6)W^*(t)+\phi_7(G(t)-\phi_6)-\phi_8 I(t).\end{aligned}$$

Suppose that

$$H(\boldsymbol{x},\boldsymbol{p}) = [\mu_1(\boldsymbol{x},\boldsymbol{p}),\mu_2(\boldsymbol{x},\boldsymbol{p}),\mu_3(\boldsymbol{x},\boldsymbol{p}),\mu_4(\boldsymbol{x},\boldsymbol{p})]^T$$

then

$$\frac{\partial H_p(\boldsymbol{x})}{\partial \boldsymbol{x}} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ -(\phi_1+\phi_2 I_R^*) & \phi_2 G & 0 & 0 \\ 0 & 0 & 1 & 0 \\ (W^*+\phi_7) & 0 & -\phi_8 & (G-\phi_6) \end{bmatrix}.$$

The four (row) vectors are linearly independent, so this matrix has Rank 4 (full rank). Therefore, the ORC is satisfied.

For $\lambda(\boldsymbol{x})$ to satisfy Eqn. (3.22) it is necessary that

$$\begin{bmatrix}1 & 0 & 1 & 0\end{bmatrix}\begin{bmatrix}\lambda_1(\boldsymbol{x}) \\ \lambda_2(\boldsymbol{x}) \\ \lambda_3(\boldsymbol{x}) \\ \lambda_4(\boldsymbol{x})\end{bmatrix} = \begin{bmatrix}1 & 0 & 1 & 0\end{bmatrix}\begin{bmatrix}G(t) \\ I_R^*(t) \\ I(t) \\ W^*(t)\end{bmatrix}.$$

Therefore,

$$\lambda_1(\boldsymbol{x}) = G(t) \tag{6.47}$$

and

$$\lambda_3(\boldsymbol{x}) = I(t) \tag{6.48}$$

and Eqn. (3.21) is then given by

$$\boldsymbol{f}(\lambda(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),\boldsymbol{p}) = \begin{bmatrix} 1 & 0 & 0 & 0 \\ \frac{\partial\lambda_2}{\partial G} & \frac{\partial\lambda_2}{\partial I_R^*} & \frac{\lambda_2}{\partial I} & \frac{\partial\lambda_2}{\partial W^*} \\ 0 & 0 & 1 & 0 \\ \frac{\partial\lambda_4}{\partial G} & \frac{\partial\lambda_4}{\partial I_R^*} & \frac{\partial\lambda_4}{\partial I} & \frac{\partial\lambda_4}{\partial W^*} \end{bmatrix} \boldsymbol{f}(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}). \tag{6.49}$$

The first component of Eqn. (6.49) is given by

$$\begin{aligned} \boldsymbol{f}_1(\lambda(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),\boldsymbol{p}) &= \mu_2(\lambda(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),\boldsymbol{p}) \\ &= \boldsymbol{f}_1(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}})),\bar{\boldsymbol{p}}) = \mu_2(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) \end{aligned}$$

giving

$$-(\phi_1 + \phi_2\lambda_2(\boldsymbol{x}))G + \phi_1 G_b = -(\bar{\phi}_1 + \bar{\phi}_2 I_R^*)G + \bar{\phi}_1\bar{G}_b.$$

Therefore, $\lambda_2(\boldsymbol{x})$ is given by

$$\lambda_2(\boldsymbol{x}) = \frac{-G\phi_1 + G\bar{\phi}_1 + GI_R^*\bar{\phi}_2 + \phi_1\phi_3 - \bar{\phi}_1\bar{\phi}_3}{G\phi_2}.$$

and

$$\frac{\partial \lambda_2(\boldsymbol{x})}{\partial G} = \frac{-\phi_1\phi_3 + \bar{\phi}_1\bar{\phi}_3}{G^2\phi_2},$$

$$\frac{\partial \lambda_2(\boldsymbol{x})}{\partial I_R} = \frac{\bar{\phi}_2}{\phi_2},$$

$$\frac{\partial \lambda_2(\boldsymbol{x})}{\partial I} = \frac{\partial \lambda_2(\boldsymbol{x})}{\partial W^*} = 0.$$

The second component of Eqn. (6.49) is satisfied if and only if

$$\boldsymbol{f}_2(\lambda(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),\boldsymbol{p}) - \frac{\partial \lambda_2}{\partial G}\boldsymbol{f}_1(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) - \frac{\partial \lambda_2}{\partial I_R^*}\boldsymbol{f}_2(\boldsymbol{x}(t,\bar{\boldsymbol{p}},\bar{\boldsymbol{p}}) = 0 \tag{6.50}$$

whereby

$$\begin{aligned} &-G^2\phi_2\phi_4 + G^2\phi_1\phi_5 - G^2\bar{\phi}_1\phi_5 + G\bar{\phi}_1\bar{\phi}_3\phi_5 + G^2\phi_2 I \\ &-G\phi_1\bar{\phi}_1\phi_3 - GI_R^*\phi_1\bar{\phi}_2\phi_3 + G\bar{\phi}_1^2\bar{\phi}_3 + GI_R^*\bar{\phi}_1\bar{\phi}_2\bar{\phi}_3 + \phi_1\bar{\phi}_1\phi_3\bar{\phi}_3 \\ &+\bar{\phi}_2\bar{\phi}_3^2 + G^2\bar{\phi}_2\bar{\phi}_4 + G^2 I_R^*\bar{\phi}_2\bar{\phi}_5 - G^2\bar{\phi}_2 I = 0 \end{aligned}$$

which satisfies Eqn. (6.50) and can be written in the form

$$\begin{aligned} &q_1(\boldsymbol{p},\bar{\boldsymbol{p}})G^2(t,\bar{\boldsymbol{p}}) + q_2(\boldsymbol{p},\bar{\boldsymbol{p}})G^2(t,\bar{\boldsymbol{p}})I_R^*(t,\bar{\boldsymbol{p}}) + q_3(\boldsymbol{p},\bar{\boldsymbol{p}})G^2(t,\bar{\boldsymbol{p}})I(t,\bar{\boldsymbol{p}}) \\ &+q_4(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}}) + q_5(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}})I_R^*(t,\bar{\boldsymbol{p}}) + q_6(\boldsymbol{p},\bar{\boldsymbol{p}}) = 0 \end{aligned}$$

for all $t \in [0,\tau)$, where

$$
\begin{aligned}
q_1(\boldsymbol{p},\bar{\boldsymbol{p}}) = &\quad -\phi_2\phi_4 + \bar{\phi}_2\bar{\phi}_4 + \phi_1\phi_5 - \bar{\phi}_1\bar{\phi}_5 \\
q_2(\boldsymbol{p},\bar{\boldsymbol{p}}) = &\quad -\bar{\phi}_2\phi_5 + \bar{\phi}_2\bar{\phi}_5 \\
q_3(\boldsymbol{p},\bar{\boldsymbol{p}}) = &\quad \phi_2 - \bar{\phi}_2 \\
q_4(\boldsymbol{p},\bar{\boldsymbol{p}}) = &\quad -\phi_1\bar{\phi}_1\phi_3 + \bar{\phi}_1^2\bar{\phi}_3 - \phi_1\phi_3\phi_5 + \bar{\phi}_1\bar{\phi}_3\phi_5 \\
q_5(\boldsymbol{p},\bar{\boldsymbol{p}}) = &\quad -\phi_1\bar{\phi}_2\phi_3 + \bar{\phi}_1\bar{\phi}_2\bar{\phi}_3 \\
q_6(\boldsymbol{p},\bar{\boldsymbol{p}}) = &\quad \phi_1\bar{\phi}_1\phi_3\bar{\phi}_3 - \bar{\phi}_1^2\bar{\phi}_3^2.
\end{aligned}
$$

This polynomial must be identically zero. Therefore each of its coefficients must be zero for all ($t \in [0, \tau)$) hence

$$q_1(\boldsymbol{p},\bar{\boldsymbol{p}}) = q_2(\boldsymbol{p},\bar{\boldsymbol{p}}) = q_3(\boldsymbol{p},\bar{\boldsymbol{p}}) = q_4(\boldsymbol{p},\bar{\boldsymbol{p}}) = q_5(\boldsymbol{p},\bar{\boldsymbol{p}}) = q_6(\boldsymbol{p},\bar{\boldsymbol{p}}) = 0.$$

Solving this system of algebraic equations, it can be concluded that

$$\bar{\phi}_5 = \phi_5 \tag{6.51}$$

$$\bar{\phi}_2 = \phi_2 \tag{6.52}$$

$$\bar{\phi}_1\bar{\phi}_3 = \phi_1\phi_3 \tag{6.53}$$

$$\phi_1\phi_5 - \bar{\phi}_1\phi_5 = \bar{\phi}_2\bar{\phi}_4 - \phi_2\phi_4. \tag{6.54}$$

As ϕ_3 is the basal level of glucose concentration (i.e. in G_b in the EMM and the CLMM), this can therefore be assumed to be known or measurable. This gives

$$\bar{\phi}_3 = \phi_3 \tag{6.55}$$

$$\bar{\phi}_1 = \phi_1 \tag{6.56}$$

$$\bar{\phi}_4 = \phi_4. \tag{6.57}$$

The third component of Eqn. (6.49) gives

$$\begin{aligned}\boldsymbol{f}_3(\lambda(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),\boldsymbol{p}) &= \mu_4(\lambda(\lambda(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),\bar{\boldsymbol{p}}) \\ &= \boldsymbol{f}_3(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) = \mu_4(\boldsymbol{x}(t,\bar{\boldsymbol{p}})\end{aligned}$$

whereby

$$(G-\phi_6)\lambda_4(\boldsymbol{x}) + \phi_7(G-\phi_6) - \phi_8 I = (G-\bar{\phi}_6)W^* + \bar{\phi}_7(G-\bar{\phi}_6) - \bar{\phi}_8 I \quad (6.58)$$

and thus

$$\lambda_4 = \frac{-G\phi_8 + \phi_7\phi_8 + G\bar{\phi}_8 - \bar{\phi}_7\bar{\phi}_8 + \phi_9 I - \bar{\phi}_9 I + G\bar{\phi}_6 W^* - \bar{\phi}_6\bar{\phi}_7 W^*}{\phi_6(G-\phi_7)}$$

and

$$\begin{aligned}\frac{\partial\lambda_4}{\partial G} &= \frac{(-\phi_9+\bar{\phi}_9)I - \phi_7(\bar{\phi}_8+\bar{\phi}_6W^*) + \bar{\phi}_7(\bar{\phi}_8+\bar{\phi}_6W^*)}{\phi_6(G-\phi_7)^2} \\ \frac{\partial\lambda_4}{\partial I_R} &= 0 \\ \frac{\partial\lambda_4}{\partial I} &= \frac{\bar{\phi}_6(G-\bar{\phi}_7)}{\phi_6(G-\phi_7)} \\ \frac{\partial\lambda_4}{\partial W^*} &= \frac{\bar{\phi}_6(G-\bar{\phi}_7)}{\phi_6(G-\phi_7)}.\end{aligned}$$

The fourth component of Eqn. (6.49) is satisfied if and only if

$$\begin{aligned}\boldsymbol{f}_4(\lambda(\boldsymbol{x}(t,\bar{\boldsymbol{p}})),\boldsymbol{p}) - \frac{\partial\lambda_4}{\partial G}\boldsymbol{f}_1(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) - \frac{\partial\lambda_4}{\partial I_R^*}\boldsymbol{f}_2(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) \\ -\frac{\partial\lambda_4}{\partial I}\boldsymbol{f}_3(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) - \frac{\partial\lambda_4}{\partial W^*}\boldsymbol{f}_4(\boldsymbol{x}(t,\bar{\boldsymbol{p}}),\bar{\boldsymbol{p}}) = 0\end{aligned} \quad (6.59)$$

whereby,

$$\begin{aligned}(G-\phi_6)\phi_9(-\phi_6\phi_7+\bar{\phi}_6\bar{\phi}_7-\phi_8 I+\bar{\phi}_8 I+G(\phi_7-\bar{\phi}_7-W^*)+\bar{\phi}_6 W^*)\\ +(G-\phi_6)(G-\bar{\phi}_6)\bar{\phi}_9 W^*-(G(\bar{\phi}_1+I_R^*\bar{\phi}_2)-\bar{\phi}_1\bar{\phi}_3)((\phi_8-\bar{\phi}_8)I\\ +\phi_6(\bar{\phi}_7+W^*)-\bar{\phi}_6(\bar{\phi}_7+W^*))+(G-\phi_6)(\phi_8-\bar{\phi}_8)(\bar{\phi}_8 I-G(\bar{\phi}_7+W^*)\\ +\bar{\phi}_6(\bar{\phi}_7+W^*))=0\end{aligned}$$

which satisfies Eqn. (6.59) and can be written in the form

$$\begin{aligned}q_1(\boldsymbol{p},\bar{\boldsymbol{p}})G^2(t,\bar{\boldsymbol{p}})+q_2(\boldsymbol{p},\bar{\boldsymbol{p}})G^2(t,\bar{\boldsymbol{p}})W^*(t,\bar{\boldsymbol{p}})+q_3(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}})\\ +q_4(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}})I_R^*(t,\bar{\boldsymbol{p}})+q_5(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}})W^*(t,\bar{\boldsymbol{p}})\\ +q_6(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}})I(t,\bar{\boldsymbol{p}})+q_7(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}})I_R^*(t,\bar{\boldsymbol{p}})I(t,\bar{\boldsymbol{p}})\\ +q_8(\boldsymbol{p},\bar{\boldsymbol{p}})G(t,\bar{\boldsymbol{p}})I_R^*(t,\bar{\boldsymbol{p}})W^*(t,\bar{\boldsymbol{p}})+q_9(\boldsymbol{p},\bar{\boldsymbol{p}})I(t,\bar{\boldsymbol{p}})\\ +q_{10}(\boldsymbol{p},\bar{\boldsymbol{p}})W^*(t,\bar{\boldsymbol{p}})+q_{11}(\boldsymbol{p},\bar{\boldsymbol{p}})=0\end{aligned} \tag{6.60}$$

for all $t\in[0,\tau)$ where

$$\begin{aligned}q_1(\boldsymbol{p},\bar{\boldsymbol{p}})=&\ \phi_8\phi_{10}-\bar{\phi}_8\bar{\phi}_{10}-\bar{\phi}_8\phi_9+\bar{\phi}_8\bar{\phi}_9\\ q_2(\boldsymbol{p},\bar{\boldsymbol{p}})=&\ -\bar{\phi}_6\phi_{10}+\bar{\phi}_6\bar{\phi}_{10}-\bar{\phi}_6\phi_9+\bar{\phi}_6\bar{\phi}_9\\ q_3(\boldsymbol{p},\bar{\boldsymbol{p}})=&\ -2\phi_7\phi_8\phi_{10}+\bar{\phi}_7\bar{\phi}_8\phi_{10}+\bar{\phi}_1\bar{\phi}_7\bar{\phi}_8+\phi_7\bar{\phi}_8\phi_{10}-\bar{\phi}_1\phi_7\bar{\phi}_8\\ &+\phi_7\bar{\phi}_8\phi_9+\bar{\phi}_7\bar{\phi}_8\phi_9-\phi_7\bar{\phi}_8\bar{\phi}_9-\bar{\phi}_7\bar{\phi}_8\bar{\phi}_9\\ q_4(\boldsymbol{p},\bar{\boldsymbol{p}})=&\ -\bar{\phi}_2\phi_7\bar{\phi}_8+\bar{\phi}_2\bar{\phi}_7\bar{\phi}_8\\ q_5(\boldsymbol{p},\bar{\boldsymbol{p}})=&\ \bar{\phi}_6\phi_7\phi_{10}-\bar{\phi}_6\phi_7\bar{\phi}_{10}-\bar{\phi}_1\bar{\phi}_6\phi_7+\bar{\phi}_6\bar{\phi}_7\phi_{10}-\bar{\phi}_6\bar{\phi}_7\bar{\phi}_{10}\\ &+\bar{\phi}_1\bar{\phi}_6\bar{\phi}_7+\bar{\phi}_6\phi_7\phi_9+\bar{\phi}_6\bar{\phi}_7\phi_9-\bar{\phi}_6\phi_7\bar{\phi}_9\bar{\phi}_6\bar{\phi}_7\bar{\phi}_9\\ q_6(\boldsymbol{p},\bar{\boldsymbol{p}})=&\ -\phi_9\phi_{10}-\bar{\phi}_1\phi_9+\bar{\phi}_9\phi_{10}+\bar{\phi}_1\bar{\phi}_9+\phi_9\bar{\phi}_9-\bar{\phi}_9^2\\ q_7(\boldsymbol{p},\bar{\boldsymbol{p}})=&\ -\bar{\phi}_2\phi_9+\bar{\phi}_2\bar{\phi}_9\\ q_8(\boldsymbol{p},\bar{\boldsymbol{p}})=&\ -\bar{\phi}_2\bar{\phi}_6\phi_7+\bar{\phi}_2\bar{\phi}_6\bar{\phi}_7\end{aligned}$$

$$
\begin{aligned}
q_9(\boldsymbol{p},\bar{\boldsymbol{p}}) = \;& \bar{\phi}_1\bar{\phi}_3\phi_9 + \phi_7\phi_9\phi_{10} - \bar{\phi}_1\bar{\phi}_3\bar{\phi}_9 - \phi_7\bar{\phi}_9\phi_{10} - \phi_7\phi_9\bar{\phi}_9 + \phi_7\bar{\phi}_9^2 \\
q_{10}(\boldsymbol{p},\bar{\boldsymbol{p}}) = \;& \bar{\phi}_1\bar{\phi}_3\bar{\phi}_6\phi_7 - \bar{\phi}_1\bar{\phi}_3\bar{\phi}_6\bar{\phi}_7 - \bar{\phi}_6\phi_7\bar{\phi}_7\phi_{10} + \bar{\phi}_6\phi_7\bar{\phi}_7\bar{\phi}_{10} \\
& -\bar{\phi}_6\phi_7\bar{\phi}_7\phi_9 + \bar{\phi}_6\phi_7\bar{\phi}_7\bar{\phi}_9 \\
q_{11}(\boldsymbol{p},\bar{\boldsymbol{p}}) = \;& \phi_7^2\phi_8\phi_{10} + \bar{\phi}_1\bar{\phi}_3\phi_7\bar{\phi}_8 - \phi_7\bar{\phi}_7\bar{\phi}_8\phi_9 + \phi_7\bar{\phi}_7\bar{\phi}_8\bar{\phi}_9 - \bar{\phi}_1\bar{\phi}_3\bar{\phi}_7\bar{\phi}_8 \\
& -\phi_7\bar{\phi}_7\bar{\phi}_8\phi_{10}.
\end{aligned}
$$

The polynomial must be identically zero. Therefore each of its coefficients must be zero for all ($t \in [0, \tau\ )$) hence

$$
\begin{aligned}
q_1(\boldsymbol{p},\bar{\boldsymbol{p}}) = q_2(\boldsymbol{p},\bar{\boldsymbol{p}}) = q_3(\boldsymbol{p},\bar{\boldsymbol{p}}) = q_4(\boldsymbol{p},\bar{\boldsymbol{p}}) = q_5(\boldsymbol{p},\bar{\boldsymbol{p}}) = q_6(\boldsymbol{p},\bar{\boldsymbol{p}}) \\
q_7(\boldsymbol{p},\bar{\boldsymbol{p}}) = q_8(\boldsymbol{p},\bar{\boldsymbol{p}}) = q_9(\boldsymbol{p},\bar{\boldsymbol{p}}) = q_{10}(\boldsymbol{p},\bar{\boldsymbol{p}}) = q_{11}(\boldsymbol{p},\bar{\boldsymbol{p}}) = 0.
\end{aligned}
$$

Solving this system of algebraic equations, it can be concluded that

$$\phi_8 = \bar{\phi}_8 \tag{6.61}$$

$$\phi_6 = \bar{\phi}_6 \tag{6.62}$$

$$-\phi_9 + \bar{\phi}_9 = \phi_8 - \bar{\phi}_8 \tag{6.63}$$

$$\phi_7\phi_9 - \bar{\phi}_7\phi_9 = \bar{\phi}_7\phi_8 - \bar{\phi}_7\bar{\phi}_8. \tag{6.64}$$

Substituting $\phi_8 = \bar{\phi}_8$, Eqn. (6.61) into Eqn. (6.63), gives

$$\phi_9 = \bar{\phi}_9. \tag{6.65}$$

Substituting $\phi_8 = \bar{\phi}_8$, Eqn. (6.61) into Eqn. (6.64), gives

$$\phi_7 = \bar{\phi}_7. \tag{6.66}$$

In conclusion, the outcomes for the parameters from the structural identifia-

bility analysis are given by

$$\phi_1 = \bar{\phi}_1,$$

$$\phi_2 = \bar{\phi}_2,$$

$$\phi_3 = \bar{\phi}_3,$$

$$\phi_4 = \bar{\phi}_4,$$

$$\phi_5 = \bar{\phi}_5,$$

$$\phi_6 = \bar{\phi}_6,$$

$$\phi_7 = \bar{\phi}_7,$$

$$\phi_8 = \bar{\phi}_8,$$

$$\phi_9 = \bar{\phi}_9$$

All the parameters of the reparameterised CLMM are uniquely identifiable if $\phi_3(\equiv G_b)$ is known, therefore the model is globally structurally identifiable.

Therefore, the reparameterised CLMM is actually globally structurally identifiable under the condition that the basal level of glucose concentration (G_b) is known.

6.5 Steady State

An analysis of the steady state of the reparameterised CLMM is subsequently carried out with Eqns. (6.40) - (6.43).

Assume, at steady state that

$$\dot{G}(t) = \dot{I}^*_R(t) = \dot{I}(t) = \dot{W}^*(t) = 0$$

Therefore, the system at steady state is given by

$$0 = -\big(\phi_1 + \phi_2 I^*_{RSS}\big)G_{RSS} + \phi_1\phi_3 \tag{6.67}$$

$$0 = I_{SS} - \phi_4 - \phi_5 I^*_{RSS} \tag{6.68}$$

$$0 = \big(G_{SS} - \phi_6\big)W^*_{SS} + \phi_7\big(G_{SS} - \phi_6\big) - \phi_8 I_{SS} \tag{6.69}$$

$$0 = -\phi_9 W^*_{SS} \tag{6.70}$$

Let G_{SS} denote the glucose concentration at steady state; I_{SS} denote the insulin concentration at steady state; I^*_{RSS} denote the insulin action at steady state and W^*_{SS} denote the dummy variable at steady state.
After rearranging, Eqn. (6.67) gives

$$G_{SS} = \frac{\phi_1\phi_3}{\phi_1 + \phi_2 I^*_{RSS}} \tag{6.71}$$

and Eqn. (6.68) gives

$$I_{SS} = \phi_4 + \phi_5 I^*_{RSS} \tag{6.72}$$

and Eqn. (6.70) gives

$$W^*_{SS} = 0. \tag{6.73}$$

Therefore, substituting Eqns. (6.71) and (6.72) into Eqn. (6.69) gives

$$\begin{aligned}\phi_8(\phi_1\phi_4 + \phi_2\phi_4 I^*_{RSS} + \phi_1\phi_5 I^*_{RSS} + \phi_2\phi_5 I^{*2}_{RSS}) - \phi_1\phi_3\phi_7 \\ -\phi_1\phi_6\phi_7 - \phi_2\phi_6\phi_7 I^*_{RSS} = 0.\end{aligned} \tag{6.74}$$

Therefore,

$$\gamma_1 I_{RSS}^{*2} + \beta_1 I_{RSS}^{*} + \alpha_1 = 0 \tag{6.75}$$

and

$$I_{RSS}^{*} = \frac{-\beta_1 \pm \sqrt{\beta_1^2 + 4\alpha_1}}{2\gamma_1} \tag{6.76}$$

where

$$\gamma_1 = \phi_1\phi_4\phi_8 - \phi_1\phi_5\phi_7 + \phi_1\phi_6\phi_7$$

$$\beta_1 = \phi_2\phi_4 + \phi_1\phi_5 + \phi_2\phi_6\phi_7$$

$$\alpha_1 = \phi_2\phi_5$$

Therefore, Eqn. (6.71) is given by

$$G_{SS} = \frac{\phi_1\phi_3}{2\phi_1\gamma_1 - \phi_2\beta_1 \pm \phi_2\sqrt{\beta_1^2 + 4\alpha_1}} \tag{6.77}$$

and Eqn. (6.72) is given by

$$I_{SS} = \phi_4 + \phi_5\left(\frac{-\beta_1 \pm \sqrt{\beta_1^2 + 4\alpha_1}}{2\gamma_1}\right) \tag{6.78}$$

Therefore, when the insulin action is not equal to zero, two non-zero steady state conditions could possibly be reached for all variables, except for dummy variable, these steady states and their nature being parameter dependent.

However, if the insulin action is assumed to be zero, $I_{RSS} = 0$. From Eqn. (6.67), the glucose concentration at steady state gives

$$G_{SS} = \phi_3, \tag{6.79}$$

and from Eqn. (6.69), insulin concentration at steady state gives

$$I_{SS} = \phi_4 \tag{6.80}$$

and the dummy variable, Eqn. (6.70) gives

$$W^*_{SS} = 0 \tag{6.81}$$

however this only occurs over infinite time as $W(t) = e^{-\lambda t} \to 0$ as $t \to \infty$.

6.6 Parameter Estimation

Parameter estimation was performed on the reparameterised CLMM, Eqns. (6.44) - (6.46) as it has been shown to be structurally globally identifiable under the condition that basal level ϕ_3 (or G_b as in the original CLMM) is known. The IVGTT data provided by Professor Leon Aarons, School of Pharmacy and Pharmaceutical Sciences, Manchester University, United Kingdom [Mills, 2007] are used again in this thesis section.

The CLMM is able to generate the first phase glucose-insulin dynamics responses as described in Chapter 2, Section 2.6. Therefore, the IVGTT data set used for the parameter estimates for CLMM includes the complete course of IVGTT experiment, including both first and second phases of glucose-insulin dynamics responses. The original IVGTT data can be used for the purpose of this parameter estimation. Table 6.1 shows the IVGTT data set for Subject 8. The parameter estimation was carried out in FACSIMILE [AEA Technology, 1995] and a list of good fits is given in Table 6.2 with RSS values and the list of well determined parameters. The corresponding plots for glucose and insulin responses for Fits 1, 2, 3 and 4 are shown in Figures 6.1, 6.2, 6.3 and 6.4 respectively. The basal levels of glucose concentration ϕ_3 and insulin

concentration ϕ_4 are assumed to be the initial or final glucose-insulin measurements. For Subject 8, basal glucose and insulin concentrations, ϕ_3 and ϕ_4 are 4.5 mmol/L and 3.2 mU/L respectively.

Fit 4 is considered to be the best fit for Subject 8 as the RSS value is the lowest at 2.7368×10^2 and all the parameters $\phi_1, \phi_2, \phi_5, \phi_6, \phi_7, \phi_8, \phi_9$ are well determined. Parameter ϕ_6 has the lowest SDLN value at 0.078 and parameters ϕ_2, ϕ_5, ϕ_7 and ϕ_8 have relatively low SDLN values ranging from 0.204 to 0.260. The parameter ϕ_1 has a rather high SDLN value at 0.794 and the parameter ϕ_9 has the highest SDLN value at 0.954 (see Table 6.3). The correlation matrix generated within Facsmile shows a high correlation between parameter estimates with, in particular, a correlation of -0.963 between ϕ_5 and ϕ_8, and moderate correlation between parameters ϕ_1 and ϕ_9 at -0.772, parameters ϕ_2 and ϕ_7 at -0.789, parameters ϕ_1 and ϕ_2 at -0.612, parameters ϕ_5 and ϕ_9 at -0.619, parameters ϕ_2 and ϕ_7 at -0.789 and parameters ϕ_8 and ϕ_9 at 0.641 (see Table 6.4). The glucose and insulin responses fitted to the IVGTT data for Fit 4 are shown in Figure 6.4.

In general, parameter ϕ_9 is not easily determined or estimated, and it is not well determined for Fits 1, 2 and 3. This may explain the high SDLN value for the parameter ϕ_9 in Fit 4. Fits 1 - 3 also demonstrate that the CLMM is able to generate first phase glucose-insulin dynamics responses. The statistical information such as SDLN values and correlation matrix for for well determined parameters for Fits 1-3 obtained within FACSMILE is given in Tables 6.3 and 6.4 and estimated glucose-insulin responses with the IVGTT data for Subject 8 are shown in Figures 6.1 - 6.3.

The parameter estimates for the CLMM show that the model has the ability to generate first phase glucose-insulin responses, especially for insulin dynamics as shown in Figures 6.1, 6.3 and 6.4. However, further work is required to achieve tighter fits and parameter estimates to IVGTT and more

Subject 8					
Time (min)	Glucose (mmol/L)	Insulin (mU/L)	Time (min)	Glucose (mmol/L)	Insulin (mU/L)
0	4.8	3.2	25	11.3	16.9
2	12.1	3.0	30	10.7	14.0
4	15.2	49.3	40	9.2	14.5
6	14.7	42.1	60	7.4	11.2
10	13.7	26.9	80	5.9	6.6
15	12.6	20.4	120	4.5	3.2
20	11.9	18.4			

Table 6.1: The IVGTT data set (Subject 8) used for the parameter estimation for the CLMM.

Fit	RSS	Parameters determined
1	$2.7314 \cdot 10^2$	$\phi_1, \phi_2, \phi_5, \phi_6, \phi_7, \phi_8$
2	$3.3628 \cdot 10^2$	$\phi_1, \phi_2, \phi_5, \phi_6, \phi_7, \phi_8$
3	$3.122 \cdot 10^2$	$\phi_1, \phi_2, \phi_5, \phi_6, \phi_7, \phi_8$
4	$2.7368 \cdot 10^2$	$\phi_1, \phi_2, \phi_5, \phi_6, \phi_7, \phi_8, \phi_9$
RSS represents the Residual Sum of Squares		

Table 6.2: List of Fits (1-4) for Subject 8 using the CLMM and the statistical information obtained within FACSIMILE , i.e. the RSS and well determined parameters.

data sets would be desirable here.

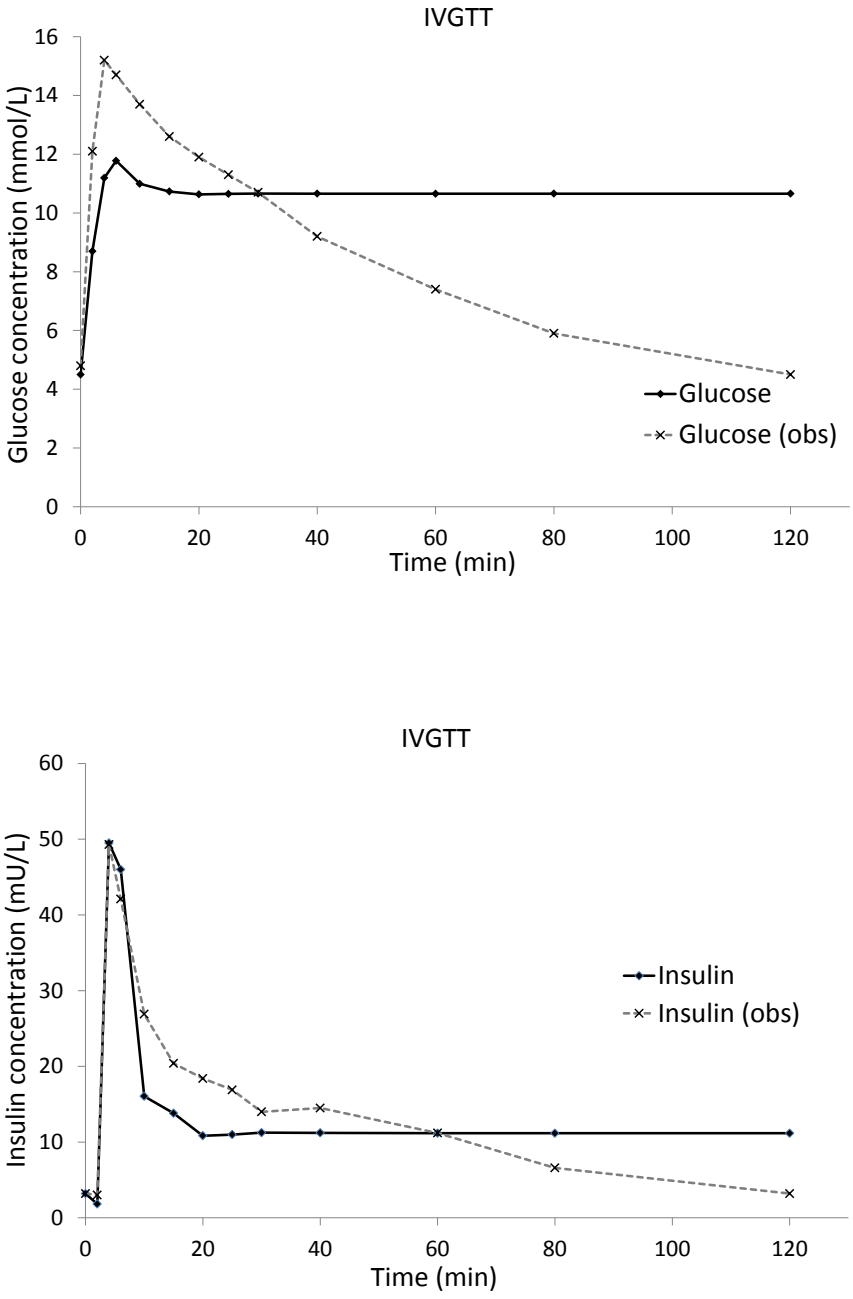

Figure 6.1: Glucose and insulin responses for the CLMM, Fit 1.

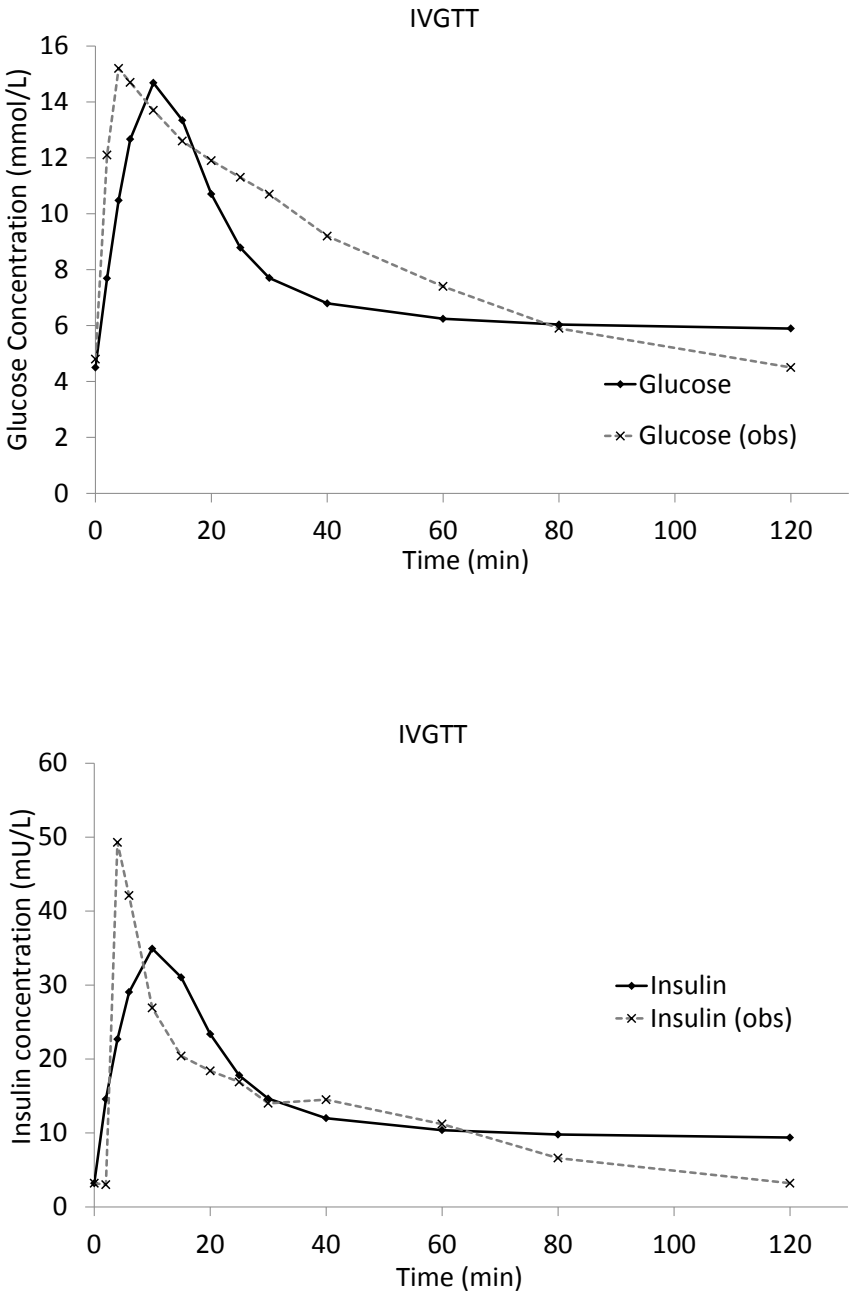

Figure 6.2: Glucose and insulin responses for the CLMM, Fit 2.

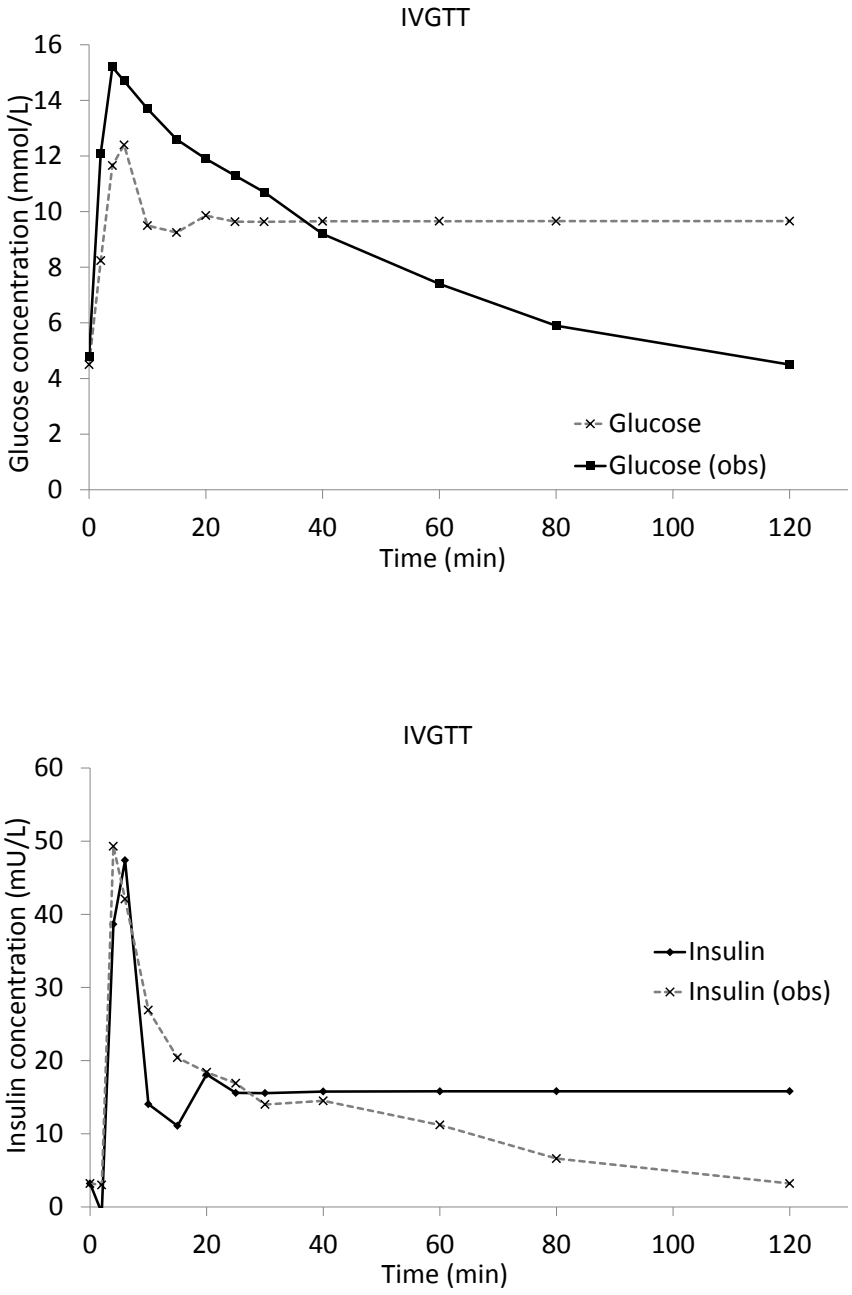

Figure 6.3: Glucose and insulin responses for the CLMM, Fit 3.

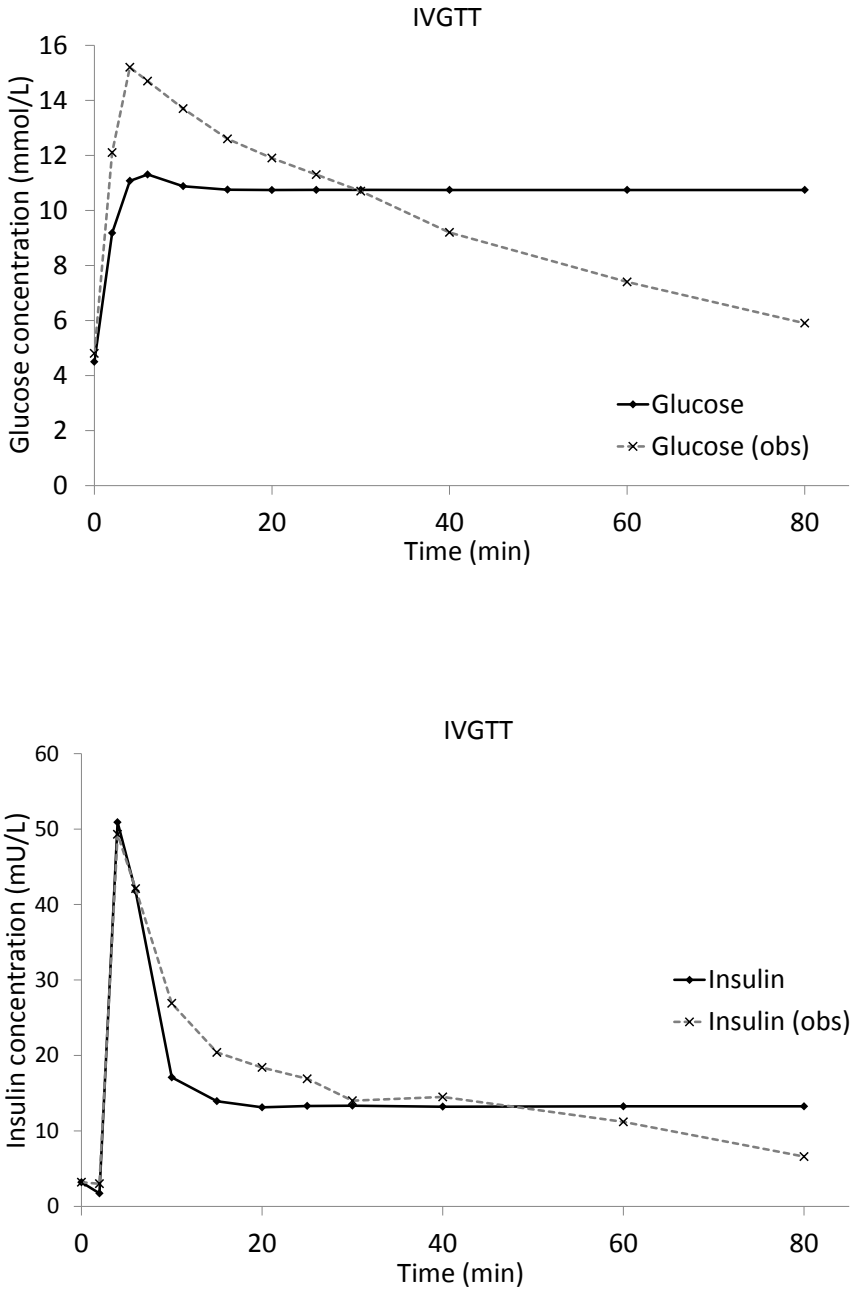

Figure 6.4: Glucose and insulin responses for the CLMM, Fit 4.

	Fit 1		Fit 2	
Parameter	Value	[SDLN]	Value	[SDLN]
ϕ_1	$2.993 \cdot 10^{-3}$	[0.254]	$3.735 \cdot 10^{-2}$	[1.756]
ϕ_2	$3.227 \cdot 10^{-2}$	[0.181]	$4.027 \cdot 10^{-4}$	[0.464]
ϕ_5	1.66	[0.134]	$8.787 \cdot 10^{-3}$	[1.593]
ϕ_6	$1.024 \cdot 10$	[0.077]	2.671	[0.917]
ϕ_7	$1.780 \cdot 10^2$	[0.191]	$5.345 \cdot 10^2$	[0.342
ϕ_8	6.666	[0.082]	$1.838 \cdot 10^2$	[0.506]
	Fit 3		Fit 4	
	Value	[SDLN]	Value	[SDLN]
ϕ_1	$6.899 \cdot 10^{-2}$	[1.688]	$6.837 \cdot 10^{-2}$	[0.794]
ϕ_2	$1.634 \cdot 10^{-3}$	[0.420]	$2.075 \cdot 10^{-2}$	[0.204]
ϕ_5	$1.515 \cdot 10^{-1}$	[0.448]	1.808	[0.246]
ϕ_6	8.283	[0.088]	$1.042 \cdot 10$	[0.078]
ϕ_7	$9.406 \cdot 10^2$	[1.917]	$2.970 \cdot 10^2$	[0.231]
ϕ_8	$8.184 \cdot 10$	[1.946]	7.188	[0.260]
ϕ_9	-	-	$6.496 \cdot 10^{-1}$	[0.954]

Table 6.3: Values and SDLNs for Fits 1, 2 and 3 (Subject 8).

Fit 1							
Row/column	ϕ_1	ϕ_2	ϕ_5	ϕ_6	ϕ_7	ϕ_8	
ϕ_1	1.000	0.482	-0.407	0.205	-0.473	0.496	
ϕ_2	0.482	1.000	-0.92	-0.15	-0.955	0.374	
ϕ_5	-0.407	-0.92	1.000	0.294	0.855	-0.372	
ϕ_6	0.205	-0.15	0.294	1.000	-0.043	0.361	
ϕ_7	-0.473	-0.955	0.855	-0.043	1.000	-0.292	
ϕ_8	0.496	0.374	-0.372	0.361	-0.292	1.000	

Fit 2							
Row/column	ϕ_1	ϕ_2	ϕ_5	ϕ_6	ϕ_7	ϕ_8	
ϕ_1	1.000	-0.788	-0.541	0.503	0.000	-0.434	
ϕ_2	-0.788	1.000	0.761	-0.487	0.252	0.596	
ϕ_5	-0.541	0.761	1.000	-0.401	0.263	0.460	
ϕ_6	0.503	-0.487	-0.401	1.000	-0.050	-0.675	
ϕ_7	0.000	0.252	0.263	-0.050	1.000	0.681	
ϕ_8	-0.434	0.596	0.460	-0.675	0.681	1.000	

Fit 3							
Row/column	ϕ_1	ϕ_2	ϕ_5	ϕ_6	ϕ_7	ϕ_8	
ϕ_1	1.000	-0.728	0.165	0.307	0.093	-0.114	
ϕ_2	-0.728	1.000	0.367	-0.079	-0.116	0.049	
ϕ_5	0.165	0.367	1.000	0.339	-0.314	-0.343	
ϕ_6	0.307	-0.079	0.339	1.000	0.040	-0.030	
ϕ_7	0.093	-0.116	-0.314	0.040	1.000	0.975	
ϕ_8	-0.114	0.049	-0.343	-0.030	0.975	1.000	

Fit 4								
Row/column	ϕ_1	ϕ_2	ϕ_5	ϕ_6	ϕ_7	ϕ_8	ϕ_9	
ϕ_1	1.000	-0.612	0.459	0.053	0.31	-0.484	-0.772	
ϕ_2	-0.612	1.000	-0.426	0.058	-0.789	0.336	0.562	
ϕ_5	0.459	-0.426	1.000	0.433	-0.165	-0.963	-0.619	
ϕ_6	0.053	0.058	0.433	1.000	-0.487	-0.381	-0.099	
ϕ_7	0.310	-0.789	-0.165	-0.487	1.000	0.264	-0.184	
ϕ_8	-0.484	0.336	-0.963	-0.381	0.264	1.000	0.641	
ϕ_9	-0.772	0.562	-0.619	-0.099	-0.184	0.641	1.000	

Table 6.4: Correlation matrixes for the well-determined parameters for Fits 1, 2, 3 and 4 (Subject 8) for the CLMM.

Chapter 7

Structural Identifiability of The Double-Pole in Closed-Loop Minimal Model

This chapter considers the structural identifiability analysis of the Double-Pole Closed-Loop Minimal Model (DPCLMM) see Chapter 2 in Section 2.7. The system equations considered for the DPCLMM are given by

$$\dot{G}(t) = -(p_1 + k_6 I_R(t))G(t) + p_1 G_b \tag{7.1}$$

$$\dot{I}_R(t) = k_2(I(t) - I_b) - p_2 I_R(t) \tag{7.2}$$

$$\dot{I}(t) = M_1(G(t) - h)e^{-\lambda t} + \gamma(G(t) - h)te^{-p_1 t} - p_{exit} I(t) \tag{7.3}$$

and the initial conditions are given by

$$G(0) = G_0 \tag{7.4}$$

$$I_R(0) = 0 \tag{7.5}$$

$$I(0) = I_0 \tag{7.6}$$

where $G(t)$ is the glucose concentration, $I(t)$ the insulin concentration and $I_R(t)$ the remote insulin action. The observations of the system are given by

$$y_1(t) = G(t) \tag{7.7}$$

$$y_2(t) = I(t). \tag{7.8}$$

A structural identifiability analysis for this model was first carried out using the Taylor Series approach. However, due to the complexity of the model structure, the structural identifiability using the Taylor Series approach has proven intractable due to the length and algebraic complexity of the coefficients generated with the approach.

Therefore, the analysis was subsequently carried out with the similarity transformation approach. Since the model is not strictly in a state space form, as the system consists of two time-dependent exponential terms and a time term, three dummy variables are required to obtain an augmented system and these are defined by the following

$$W(t) = e^{-\lambda t} \tag{7.9}$$

$$Z(t) = e^{-p_1 t} \tag{7.10}$$

$$R(t) = t. \tag{7.11}$$

Therefore, an augmented version of DPCLMM can be generated for the structural identifiability analysis using a version of Similarity Transformation Approach for an autonomous system [Evans et al., 2005] and the system equations

are given by

$$\dot{G}(t) = -(p_1 + k_6 I_R(t))G(t) + p_1 G_b \tag{7.12}$$

$$\dot{I}_R(t) = k_2(I(t) - I_b) - p_2 I_R(t) \tag{7.13}$$

$$\dot{I}(t) = M_1(G(t) - h)W(t) + \gamma(G(t) - h)RZ(t) - p_{exit} I(t) \tag{7.14}$$

$$\dot{R}(t) = 1 \tag{7.15}$$

$$\dot{W}(t) = -\lambda W(t) \tag{7.16}$$

$$\dot{Z}(t) = -p_1 Z(t) \tag{7.17}$$

and the corresponding initial conditions are given by

$$G(0) = G_b \tag{7.18}$$

$$I(0) = I_b \tag{7.19}$$

$$I_R(0) = 0 \tag{7.20}$$

$$R(0) = 0 \tag{7.21}$$

$$W(0) = 1 \tag{7.22}$$

$$Z(0) = 1. \tag{7.23}$$

As the augmented DPCLMM is not controllable, the approach for an autonomous system [Evans et al., 2002] is considered where Theorem 3.1.5 is applied.

The ORC is tested for initially. First, consider

$$\mu_1(\boldsymbol{x}) = G(t) \tag{7.24}$$

then choose

$$\mu_2(\boldsymbol{x}) = L_{fp}\mu_1(\boldsymbol{x}) \tag{7.25}$$

$$= -(p_1 + k_6 I_R(t))G(t) + p_1 G_b \tag{7.26}$$

and

$$\mu_3(\boldsymbol{x}) = L_{fp}\mu_2(\boldsymbol{x}) \tag{7.27}$$

$$= (-p_1 - k_6 I_R(t))(G_b p_1 + G(t)(-p_1 - k_6 I_R(t))) \tag{7.28}$$

$$- k_6 G(t)(-p_2 I_R(t) + k_2(-I_b + I(t))).$$

Then consider,

$$\mu_4(\boldsymbol{x}, \boldsymbol{p}) = I(t) \tag{7.29}$$

and choose

$$\mu_5(\boldsymbol{x}, \boldsymbol{p}) = L_{fp}\mu_4(\boldsymbol{x}) \tag{7.30}$$

$$= -M_1(G(t) - h)W(t) + \gamma(G(t) - h)R(t)Z(t) - p_{exit}I(t). \tag{7.31}$$

and choose

$$\mu_6(\boldsymbol{x}, \boldsymbol{p}) = L_{fp}\mu_5(\boldsymbol{x}) \tag{7.32}$$

$$= p_{exit}^2 I(t) + M_1(G_b p_1 - h(\lambda - p_{exit}) - G(t)(\lambda + p_1 + p_{exit} \tag{7.33}$$

$$- k_6 I_R(t)))W(t) + \gamma(-h + (G_b p_1 + h(p_1 + p_{exit}))R(t)$$

$$- G(t)(-1 + (2p_1 + p_{exit} + k_6 I_R(t))R(t)))Z(t).$$

Suppose that

$$H(\boldsymbol{x}, \boldsymbol{p}) = [\mu_1(\boldsymbol{x}, \boldsymbol{p}), \mu_2(\boldsymbol{x}, \boldsymbol{p}), \mu_3(\boldsymbol{x}, \boldsymbol{p}), \mu_4(\boldsymbol{x}, \boldsymbol{p}), \mu_5(\boldsymbol{x}, \boldsymbol{p}), \mu_6(\boldsymbol{x}, \boldsymbol{p})]^T \tag{7.34}$$

then

$$\frac{\partial H_p(\boldsymbol{x})}{\partial \boldsymbol{x}} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ -p_1 - k_6 I_R(t) & -k_6 G(t) & 0 & 0 & 0 & 0 \\ a_{3,1} & a_{3,2} & -k_2 k_6 G(t) & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ a_{5,1} & 0 & -p_{exit} & a_{5,4} & a_{5,5} & a_{5,6} \\ a_{6,1} & a_{6,2} & p_{exit}^2 & a_{6,4} & a_{6,5} & a_{6,6} \end{bmatrix} \tag{7.35}$$

where

$$a_{3,1} = I_b k_2 k_6 + p_1^2 + k_6(2p_1 + p_2) I_R(t) + k_6^2 I_R^2(t) - k_2 k_6 I(t) \tag{7.36}$$

$$a_{3,2} = k_6(-G_b p_1 + G(t)(2p_1 + p_2 + 2k_6 I_R(t))) \tag{7.37}$$

$$a_{5,1} = M_1 W(t) + \gamma R(t) Z(t) \tag{7.38}$$

$$a_{5,4} = \gamma(-h + G(t)) Z(t) \tag{7.39}$$

$$a_{5,5} = M_1(-h + G(t)) \tag{7.40}$$

$$a_{5,6} = \gamma(-h + G(t)) R(t) \tag{7.41}$$

$$\begin{aligned} a_{6,1} = &- M_1 W(t)(\lambda + p_1 + p_{exit} + k_6 I_R(t)) \\ &- \gamma Z(t)(-1 + R(t)(2p_1 + p_{exit} + k_6 I_R(t))) \end{aligned} \tag{7.42}$$

$$a_{6,2} = - k_6 M_1 G(t) W(t) - \gamma k_6 G(t) R(t) Z(t) \tag{7.43}$$

$$\begin{aligned} a_{6,4} = &- \gamma p_1 (G(t) - h) Z(t) - \gamma p_{exit} (G(t) - h) Z(t) \\ &+ \gamma(G_b p_1 + G(t)(-p_1 - k_6 I_R(t))) Z(t) \end{aligned} \tag{7.44}$$

$$\begin{aligned} a_{6,5} = &- \lambda M_1 (G(t) - h) - M_1 p_{exit} (G(t) - h) \\ &+ M_1(G_b p_1 + G(t)(-p_1 - k_6 I_R(t))) \end{aligned} \tag{7.45}$$

$$\begin{aligned} a_{6,6} = &\gamma(G(t) - h) - \gamma p_1 (G(t) - h) R(t) - \gamma p_{exit} (G(t) - h) R(t) \\ &+ \gamma(G_b p_1 + G(t)(-p_1 - k_6 I_R(t)) R(t). \end{aligned} \tag{7.46}$$

Consider (7.35) when $t = 0$,

$$\frac{\partial H_p(\boldsymbol{x})}{\partial \boldsymbol{x}} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ -p_1 & -G_0 k_6 & 0 & 0 & 0 & 0 \\ b_{3,1} & b_{3,2} & b_{3,3} & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ M_1 & 0 & -p_{exit} & b_{4,4} & b_{4,5} & 0 \\ b_{6,1} & b_{6,2} & b_{6,3} & b_{6,4} & b_{6,5} & b_{6,6} \end{bmatrix} \tag{7.47}$$

$$b_{3,1} = p_1^2 - k_2 k_6(-I_b + I_0) \tag{7.48}$$

$$b_{3,2} = G_0 k_6 p_1 - k_6(-G_0 p_1 + G_b p_1) + G_0 k_6 p_2 \tag{7.49}$$

$$b_{3,3} = -G_0 k_2 k_6 \tag{7.50}$$

$$b_{4,4} = \gamma(G_0 - h) \tag{7.51}$$

$$b_{4,5} = (G_0 - h) M_1 \tag{7.52}$$

$$b_{6,1} = \gamma - \lambda M_1 - M_1 p_1 - M_1 p_{exit} \tag{7.53}$$

$$b_{6,2} = -G_0 k_6 M_1 \tag{7.54}$$

$$b_{6,3} = p_{exit}^2 \tag{7.55}$$

$$b_{6,4} = -\gamma(G_0 - h) p_1 + \gamma(-G_0 p_1 + G_b p_1) - \gamma(G_0 - h) p_{exit} \tag{7.56}$$

$$b_{6,5} = -(G_0 - h)\lambda M_1 + M_1(-G_0 p_1 + G_b p_1) - (G_0 - h) M_1 p_{exit} \tag{7.57}$$

$$b_{6,6} = \gamma(G_0 - h). \tag{7.58}$$

By using a symbolic computational tool, Mathematica, it can be shown that the rank of (7.35) and (7.47) are 5 (< 6). Therefore, the model is not observable. Therefore, Theorem 3.1.5 cannot be applied to the DPCLMM as it does not satisfy the ORC.

As the ORC is not satisfied, the structural identifiability using the Simi-

larity Transformation approach cannot be proceeded. Therefore, the structural identifiability of the model remained unsolved or unknown.

Chapter 8

Structural Indinstinguishability Analysis

8.1 Introduction

The structural indistinguishability analyses in this chapter are performed on the glucose-insulin dynamics models considered in this thesis with the same observations, i.e. glucose and insulin concentrations, to find out if these models can be distinguished from each other given the same experimental output. In the case that the models are indistinguishable from each other, it is not possible to tell the difference between models from their observations alone.

A structural indistinguishability analysis for the EMM and the CLMM is considered, as the CLMM is a modified version of EMM and therefore these two models have similar model structures. Besides that, the EMM is a widely referenced model, it is important to determine whether the EMM and CLMM are distinguishable with the same system observations. The analyses are carried out based on the assumptions that IVGTTs are applied to the models and that the system observations are of glucose and insulin concentrations.

8.2 The Structural Indistinguishability Analysis of the CLMM and EMM over The Post-Switching Phase

A structural indistinguishability analysis for the CLMM and the EMM over the post-switching phase is performed using the Taylor Series approach. The system equations of EMM over post-switching phase are given by

$$\dot{G}(t) = -[p_1 + X(t)]G(t) + p_1 G_b \tag{8.1}$$

$$\dot{X}(t) = -p_2 X(t) + p_3[I(t) - I_b] \tag{8.2}$$

$$\dot{I}(t) = -p_6[I(t) - I_b] \qquad G(t) < p_5 \tag{8.3}$$

and system equations of the CLMM are given by

$$\dot{\tilde{G}}(t) = -(\tilde{\phi}_1 + \tilde{\phi}_2 \tilde{I}^*_R(t))\tilde{G}(t) + \tilde{\phi}_1\tilde{\phi}_3 \tag{8.4}$$

$$\dot{\tilde{I}}^*_R(t) = \tilde{I} - \tilde{\phi}_4 - \tilde{\phi}_5 \tilde{I}^*_R(t) \tag{8.5}$$

$$\dot{\tilde{I}}(t) = (\tilde{G}(t) - \tilde{\phi}_6)\exp(-\tilde{\phi}_9 t) + \tilde{\phi}_7(\tilde{G}(t) - \tilde{\phi}_6) - \tilde{\phi}_8\tilde{I}(t). \tag{8.6}$$

Initial conditions for the EMM are given by

$$G(0) = G_0 \tag{8.7}$$

$$X(0) = 0 \tag{8.8}$$

$$I(0) = I_0 \tag{8.9}$$

and initial conditions for the CLMM are given by

$$\tilde{G}(0) = \tilde{G}_0 \tag{8.10}$$

$$\tilde{I}_R^*(0) = 0 \tag{8.11}$$

$$\tilde{I}(0) = \tilde{I}_0. \tag{8.12}$$

The observations of the systems are given by

$$y_1(t) = G(t) \tag{8.13}$$

$$y_2(t) = I(t) \tag{8.14}$$

$$\tilde{y}_1(t) = \tilde{G}(t) \tag{8.15}$$

$$\tilde{y}_2(t) = \tilde{I}(t). \tag{8.16}$$

The first Taylor Series coefficients and their evaluations at $t = 0$ are given by

$$y_1(0) = G_0 \tag{8.17}$$

$$y_2(0) = I_0 \tag{8.18}$$

$$\tilde{y}_1(0) = \tilde{G}_0 \tag{8.19}$$

$$\tilde{y}_2(0) = \tilde{I}_0. \tag{8.20}$$

Therefore,

$$G_0 = \tilde{G}_0 \tag{8.21}$$

$$I_0 = \tilde{I}_0. \tag{8.22}$$

The second Taylor Series coefficients and their evaluations at $t = 0$ are given

by

$$\dot{y}_1(0) = -G_0 p_1 + G_b p_1 \tag{8.23}$$

$$\dot{y}_2(0) = -p_6(-I_b + I_0) \tag{8.24}$$

$$\dot{\tilde{y}}_1(0) = -\tilde{G}_0\tilde{\phi}_1 + \tilde{\phi}_1\tilde{\phi}_3 \tag{8.25}$$

$$\dot{\tilde{y}}_2(0) = \tilde{G}_0 - \tilde{\phi}_6 + (\tilde{G}_0 - \tilde{\phi}_6)\tilde{\phi}_7 - \tilde{\phi}_8\tilde{I}_0. \tag{8.26}$$

As the parameter ϕ_3 is the basal level of glucose concentration, (Chapter 6 Section 6.4) and is assumed to be known *a priori* for both models therefore

$$\tilde{\phi}_3 = G_b. \tag{8.27}$$

As $\dot{y}_1(0) = \dot{\tilde{y}}_1(0)$, equating the RHS of (8.23) and (8.25) after substituting in (8.21) and $G_b = \tilde{\phi}_3$ (from Chapter 6 Section 6.4), this gives

$$\tilde{\phi}_1 = p_1. \tag{8.28}$$

As $\dot{y}_2(0) = \tilde{\dot{y}}_2(0)$, comparing the RHS of Eqns. (8.24) and (8.26), after substituting in (8.21) and (8.22) gives

$$-p_6(-I_b + \tilde{I}_0) = \tilde{G}_0 - \tilde{\phi}_6 + (\tilde{G}_0 - \tilde{\phi}_6)\tilde{\phi}_7 - \tilde{\phi}_8\tilde{I}_0 \tag{8.29}$$

whereby

$$\tilde{\phi}_7 = \frac{\tilde{G}_0 + I_b p_6 + \tilde{\phi}_6\tilde{I}_0 + \tilde{\phi}_8\tilde{I}_0}{\tilde{G}_0 - \tilde{\phi}_6}. \tag{8.30}$$

The third Taylor Series coefficients and their evaluation at $t = 0$ gives:

$$\ddot{y}_1(0) = -\, p_1\dot{y}_1(0) - G_0p_3(-I_b + I_0) \tag{8.31}$$

$$\ddot{y}_2(0) = -\, p_6\dot{y}_2(0) \tag{8.32}$$

$$\dddot{\tilde{y}}_1(0) = -\, \tilde{G}_0\tilde{\phi}_2(-\tilde{\phi}_4 + \tilde{I}_0 - \tilde{\phi}_5\tilde{I}_0) - \tilde{\phi}_1\ddot{\tilde{y}}_1(0) \tag{8.33}$$

$$\dddot{\tilde{y}}_2(0) = \ddot{\tilde{y}}_1(0) + \dot{\tilde{y}}_1(0)\tilde{\phi}_7 - (\tilde{G}_0 - \tilde{\phi}_6)\tilde{\phi}_9 - \tilde{\phi}_8\ddot{\tilde{y}}_2(0). \tag{8.34}$$

As as $\ddot{y}_1(0) = \dddot{\tilde{y}}_1(0)$, comparing the RHS of Eqns. (8.31) and (8.33) after substituting in $\dot{y}_1(0) = \ddot{\tilde{y}}_1(0)$ and (8.21), (8.22) and (8.28) gives

$$\tilde{\phi}_2 = \frac{p_3(I_b - \tilde{I}_0)}{\tilde{\phi}_4 - \tilde{I}_0 + \tilde{\phi}_5\tilde{I}_0}. \tag{8.35}$$

As $\ddot{y}_2(0) = \dddot{\tilde{y}}_2(0)$, comparing (8.32) and (8.34), substituting in $\dot{y}_1(0) = \ddot{\tilde{y}}_1(0)$, $\dot{y}_2(0) = \ddot{\tilde{y}}_2(0)$, (8.21), (8.22), (8.27), (8.30), gives

$$\begin{aligned}\tilde{\phi}_9 =& \frac{1}{(\tilde{G}_0 - \tilde{\phi}_6)^2}(I_bp_6\ddot{\tilde{y}}_1(0) - p_6\tilde{I}_0\ddot{\tilde{y}}_1(0) + \tilde{\phi}_8\tilde{I}_0\ddot{\tilde{y}}_1(0) + \tilde{G}_0p_6\ddot{\tilde{y}}_2(0) \\ & - p_6\tilde{\phi}_6\ddot{\tilde{y}}_2(0) - \tilde{G}_0\tilde{\phi}_8\ddot{\tilde{y}}_2(0) + \tilde{\phi}_6\tilde{\phi}_8\ddot{\tilde{y}}_2(0)).\end{aligned} \tag{8.36}$$

The fourth coefficients of Taylor Series and their evaluations at $t = 0$ give

$$\begin{aligned}\dddot{y}_1(0) =& -\, 2p_3\dot{y}_1(0)(-I_b + \tilde{I}_0) - G_0(-p_2p_3(I_0 - I_b) + p_3\dot{y}_2(0)) \\ & - \tilde{\phi}_1\ddot{y}_1(0)\end{aligned} \tag{8.37}$$

$$\dddot{y}_2(0) = -\, p_6\ddot{y}_2(0) \tag{8.38}$$

$$\begin{aligned}\dddot{\tilde{y}}_1(0) =& -\, 2\tilde{\phi}_2\ddot{\tilde{y}}_1(0)(I_0 - \tilde{\phi}_4 - \tilde{\phi}_5I_0) - \tilde{\phi}_2G_0(\ddot{\tilde{y}}_2(0) - \tilde{\phi}_5\ddot{\tilde{y}}_2(0)) \\ & - \tilde{\phi}_1\dddot{\tilde{y}}_1(0)\end{aligned} \tag{8.39}$$

$$\dddot{\tilde{y}}_2(0) = \tilde{\phi}_9^2(-\tilde{\phi}_6 + \tilde{G}_0) - 2\tilde{\phi}_9\ddot{\tilde{y}}_1(0) + \dddot{\tilde{y}}_1(0) + \tilde{\phi}_7\dddot{\tilde{y}}_1(0) - \tilde{\phi}_8\dddot{\tilde{y}}_2(0) \tag{8.40}$$

As $\ddot{\tilde{y}}_1(0) = \dddot{\tilde{y}}_1(0)$, comparing the RHS of (8.37) and (8.39) after substituting $\ddot{y}_1(0) = \ddot{\tilde{y}}_1(0)$, $\dot{y}_1(0) = \dot{\tilde{y}}_1(0)$, $\dot{y}_2(0) = \dot{\tilde{y}}_2(0)$, (8.21), (8.22), (8.27), (8.28), (8.35) gives

$$p_3 = 0. \tag{8.41}$$

Since generically $p_3 \neq 0$ this provides a contradiction, hence the outputs for the EMM and CLMM are not consistent and the two models are therefore distinguishable over the pre-switching phase.

8.3 The Structural Indistinguishability Analysis of the CLMM and EMM Over the Pre-Switching Phase

A structural indistinguishability analysis of the EMM and the CLMM is performed using Taylor Series approach. The system equations for the EMM over the pre-switching phase are given by:

$$\dot{G}(t) = -[p_1 + X(t)]G(t) + p_1 G_b \tag{8.42}$$

$$\dot{X}(t) = -p_2 X(t) + p_3[I(t) - I_b] \tag{8.43}$$

$$\dot{I}(t) = p_4 t[G(t) - p_5] - p_6[I(t) - I_b] \tag{8.44}$$

and the system equations of the CLMM are given by:

$$\dot{\tilde{G}}(t) = -(\tilde{\phi}_1 + \tilde{\phi}_2 \tilde{I}_R^*(t))\tilde{G}(t) + \tilde{\phi}_1 \tilde{\phi}_3 \tag{8.45}$$

$$\dot{\tilde{I}}_R^*(t) = \tilde{I} - \tilde{\phi}_4 - \tilde{\phi}_5 \tilde{I}_R^*(t) \tag{8.46}$$

$$\dot{\tilde{I}}(t) = (\tilde{G}(t) - \tilde{\phi}_6)\exp(-\tilde{\phi}_9 t) + \tilde{\phi}_7(\tilde{G}(t) - \tilde{\phi}_6) - \tilde{\phi}_8 \tilde{I}(t). \tag{8.47}$$

The initial conditions of the EMM are given by

$$G(0) = G_0 \tag{8.48}$$

$$X(0) = 0 \tag{8.49}$$

$$I(0) = I_0 \tag{8.50}$$

and the initial conditions of the CLMM are given by

$$\tilde{G}(0) = \tilde{G}_0 \tag{8.51}$$

$$\tilde{I}_R^*(0) = 0 \tag{8.52}$$

$$\tilde{I}(0) = \tilde{I}_0. \tag{8.53}$$

The observations of EMM are

$$y_1(t) = G(t) \tag{8.54}$$

$$y_2(t) = I(t) \tag{8.55}$$

and the observations of CLMM are

$$\tilde{y}_1(t) = \tilde{G}(t) \tag{8.56}$$

$$\tilde{y}_2(t) = \tilde{I}(t). \tag{8.57}$$

The first coefficients of the relative Taylor Series expansions at $t = 0$ are given by

$$y_1(0) = G_0 \tag{8.58}$$

$$y_2(0) = I_0 \tag{8.59}$$

$$\tilde{y}_1(0) = \tilde{G}_0 \tag{8.60}$$

$$\tilde{y}_2(0) = \tilde{I}_0. \tag{8.61}$$

Therefore,

$$G_0 = \tilde{G}_0 \tag{8.62}$$

$$I_0 = \tilde{I}_0. \tag{8.63}$$

The second coefficients of the Taylor Series expansions and their evaluations at $t = 0$ are given by

$$\dot{y}_1(0) = -p_1 G_0 + p_1 G_b \tag{8.64}$$

$$\dot{y}_2(0) = -p_6(I_0 - I_b) \tag{8.65}$$

$$\dot{\tilde{y}}_1(0) = -\tilde{G}_0\tilde{\phi}_1 + \tilde{\phi}_1\tilde{\phi}_3 \tag{8.66}$$

$$\dot{\tilde{y}}_2(0) = \tilde{G}_0 - \tilde{\phi}_6 + (\tilde{G}_0 - \tilde{\phi}_6)\tilde{\phi}_7 - \tilde{I}_0\tilde{\phi}_8. \tag{8.67}$$

Comparing the observations of the system, (8.64) and (8.66), which are assumed to be equivalent gives

$$-p_1 G_0 + p_1 G_b = -\tilde{G}_0\tilde{\phi}_1 + \tilde{\phi}_1\tilde{\phi}_3. \tag{8.68}$$

After substituting (8.27), (8.62) and (8.63) gives

$$p_1 = \tilde{\phi}_1. \tag{8.69}$$

Comparing the observations of the system, (8.65) and (8.67), and after substituting (8.62) and (8.63) as known parameters consistent in both models gives

$$-p_6(I_0 - \tilde{I}_b) = G_0 - \tilde{\phi}_6 + (G_0 - \tilde{\phi}_6)\tilde{\phi}_7 - I_0\tilde{\phi}_8. \tag{8.70}$$

whereby

$$p_6 = \frac{\tilde{G}_0 - \tilde{\phi}_6 + \tilde{G}_0\tilde{\phi}_7 - \tilde{\phi}_6\tilde{\phi}_7 - \tilde{\phi}_8\tilde{I}_0}{I_b - \tilde{I}_0} \tag{8.71}$$

The third coefficients of the Taylor Series expansions and their evaluations at $t = 0$ are given by

$$\ddot{y}_1(0) = - p_1\dot{y}_1(0) - G_0p_3(-I_b + I_0) \tag{8.72}$$

$$\ddot{y}_2(0) = p_4(G_0 - p_5) - p_6\dot{y}_2(0) \tag{8.73}$$

$$\dddot{\tilde{y}}_1(0) = - \tilde{G}_0\tilde{\phi}_2(-\tilde{\phi}_4 + \tilde{I}_0 - \tilde{\phi}_5\tilde{I}_0) - \tilde{\phi}_1\dot{\tilde{y}}_1(0) \tag{8.74}$$

$$\dddot{\tilde{y}}_2(0) = - (\tilde{G}_0 - \tilde{\phi}_6)\tilde{\phi}_9 + \dot{\tilde{y}}_1(0) + \tilde{\phi}_7\dot{\tilde{y}}_1(0) - \tilde{\phi}_8\dot{\tilde{y}}_2(0). \tag{8.75}$$

As the observations $\ddot{y}_1(0) = \dddot{\tilde{y}}_1(0)$, equating the RHS of (8.72) and (8.74) after substituting in (8.62), (8.63) and (8.69) gives

$$p_3 = \frac{\tilde{\phi}_2(\tilde{\phi}_4 - \tilde{I}_0 + \tilde{\phi}_5\tilde{I}_0)}{I_b - \tilde{I}_0}. \tag{8.76}$$

As the observations $\ddot{y}_2(0) = \dddot{\tilde{y}}_2(0)$, equating the RHS of (8.73) and (8.75) after substituting in (8.62), (8.63) and (8.71) gives,

$$p_4 = \frac{1}{\tilde{G}_0 - p_5}\left(\dot{\tilde{y}}_1(0) + \dot{\tilde{y}}_1(0)\tilde{\phi}_7 - (\tilde{G}_0 - \tilde{\phi}_6)\tilde{\phi}_9 - \tilde{\phi}_8\dot{\tilde{y}}_2(0) - \frac{\dot{\tilde{y}}_2^2(0)}{(I_b - \tilde{I}_0)^2}\right). \tag{8.77}$$

The fourth coefficients of the Taylor Series expansions and their evaluations

at $t = 0$ are given by

$$\dddot{y}_1(0) = -2p_3(-I_b + I_0)\dot{y}_1(0) - G_0(-p_2p_3(-I_b + I_0) + p_3\dot{y}_2(0)) - p_1\ddot{y}_1(0) \tag{8.78}$$

$$\dddot{y}_2(0) = 2p_4\dot{y}_1(0) - p_6\ddot{y}_2(0) \tag{8.79}$$

$$\dddot{\tilde{y}}_1(0) = -2\tilde{\phi}_2\dot{\tilde{y}}_1(0)(-\tilde{\phi}_4 + \tilde{I}_0 - \tilde{\phi}_5\tilde{I}_0) - \tilde{\phi}_1\ddot{\tilde{y}}_1(0) - \tilde{G}_0\tilde{\phi}_2\dot{\tilde{y}}_2(0)(1 - \tilde{\phi}_5) \tag{8.80}$$

$$\dddot{\tilde{y}}_2(0) = -(\tilde{G}_0 - \tilde{\phi}_6)\tilde{\phi}_9^2 - 2\tilde{\phi}_9\dot{\tilde{y}}_1(0) + \ddot{\tilde{y}}_1(0) + \tilde{\phi}_7\ddot{\tilde{y}}_1(0) - \tilde{\phi}_8\ddot{\tilde{y}}_2(0). \tag{8.81}$$

As $\dddot{y}_1(0) = \dddot{\tilde{y}}_1(0)$, equating the RHS of (8.78) and (8.80) after substituting in (8.62), (8.63), (8.69), (8.76) and (8.77) gives

$$I_b = \frac{-\tilde{G}_0\tilde{\phi}_4(1 + \tilde{\phi}_7) + p_2\tilde{I}_0^2(\tilde{\phi}_5 - 1) + \tilde{\phi}_4(\tilde{\phi}_6 + \tilde{\phi}_6\tilde{\phi}_7 + p_2\tilde{I}_0 + \tilde{\phi}_8\tilde{I}_0)}{\tilde{G}_0(\tilde{\phi}_5 - 1)(1 + \tilde{\phi}_7) + p_2(\tilde{\phi}_4 + \tilde{I}_0(\tilde{\phi}_5 - 1)) - (\tilde{\phi}_5 - 1)(\tilde{\phi}_6 + \tilde{\phi}_6\tilde{\phi}_7 + \tilde{\phi}_8\tilde{I}_0)}. \tag{8.82}$$

As $\dddot{y}_2(0) = \dddot{\tilde{y}}_2(0)$, equating the RHS of (8.79) and (8.81) after substituting

(8.62), (8.63), (8.69), (8.76) and (8.77) in gives

$$
\begin{aligned}
p_5 =&\bar{G}_0^3(-1+\bar{\phi}_5)(1+\bar{\phi}_7)(\bar{\phi}_1(1+\bar{\phi}_7)-(1+\bar{\phi}_7)\bar{\phi}_8-\bar{\phi}_9) \\
&+2\bar{\phi}_1\bar{\phi}_3(\bar{\phi}_6^2+\bar{\phi}_5\bar{\phi}_6^2+2\bar{\phi}_6^2\bar{\phi}_7-2\bar{\phi}_5\bar{\phi}_6^2\bar{\phi}_7++\bar{\phi}_6^2\bar{\phi}_7^2-\bar{\phi}_5\bar{\phi}_6^2\bar{\phi}_7^2 \\
&+\bar{\phi}_4\bar{\phi}_6\bar{\phi}_8+\bar{\phi}_4\bar{\phi}_6\bar{\phi}_7\bar{\phi}_8+\bar{\phi}_4\bar{\phi}_6\bar{\phi}_9+\bar{\phi}_6\bar{\phi}_8\bar{I}_0-\bar{\phi}_5\bar{\phi}_6\bar{\phi}_8\bar{I}_0 \\
&+\bar{\phi}_6\bar{\phi}_7\bar{\phi}_8\bar{I}_0-\bar{\phi}_5\bar{\phi}_6\bar{\phi}_7\bar{\phi}_8\bar{I}_0+\bar{\phi}_4\bar{\phi}_8^2\bar{i}_0-\bar{\phi}_6\bar{\phi}_9\bar{I}_0+\bar{\phi}_5\bar{\phi}_6\bar{\phi}_9\bar{I}_0 \\
&+\bar{\phi}_1\bar{\phi}_3(1+\bar{\phi}_7)(\bar{\phi}_4+(-1+\bar{\phi}_5)\bar{I}_0) \\
&+p_2(\bar{\phi}_4+(-1+\bar{\phi}_5)\bar{I}_0)(\bar{\phi}_6+\bar{\phi}_6\bar{\phi}_7+\bar{\phi}_8\bar{I}_0))+\bar{G}_0^2(-p_2\bar{\phi}_4\bar{\phi}_8 \\
&-2\bar{\phi}_6\bar{\phi}_8+2\bar{\phi}_5\bar{\phi}_6\bar{\phi}_8-p_2\bar{\phi}_4\bar{\phi}_7\bar{\phi}_8-4\bar{\phi}_6\bar{\phi}_7\bar{\phi}_8+2\bar{\phi}_5\bar{\phi}_6\bar{\phi}_7\bar{\phi}_8 \\
&-2\bar{\phi}_6\bar{\phi}_7^2\bar{\phi}_8+2\bar{\phi}_5\bar{\phi}_6\bar{\phi}_7^2\bar{\phi}_8-\bar{\phi}_4\bar{\phi}_8^2-\bar{\phi}_4\bar{\phi}_7\bar{\phi}_8^2-p_2\bar{\phi}_4\bar{\phi}_9 \\
&-2\bar{\phi}_6\bar{\phi}_9+2\bar{\phi}_5\bar{\phi}_6\bar{\phi}_9-2\bar{\phi}_6\bar{\phi}_7\bar{\phi}_9+2\bar{\phi}_5\bar{\phi}_6\bar{\phi}_7\bar{\phi}_9-\bar{\phi}_4\bar{\phi}_8\bar{\phi}_9 \\
&+\bar{\phi}_4\bar{\phi}_9^2+p_2\bar{\phi}_8\bar{I}_0-p_2\bar{\phi}_5\bar{\phi}_8\bar{I}_0+p_2\bar{\phi}_7\bar{\phi}_8\bar{I}_0-p_2\bar{\phi}_5\bar{\phi}_7\bar{\phi}_8\bar{I}_0 \\
&-\bar{\phi}_8^2\bar{I}_0+\bar{\phi}_5\bar{\phi}_8^2\bar{I}_0-\bar{\phi}_7\bar{\phi}_8^2\bar{I}_0+\bar{\phi}_6\bar{\phi}_7\bar{\phi}_8^2\bar{I}_0+p_2\bar{\phi}_9\bar{I}_0-p_2\bar{\phi}_5\bar{\phi}_9\bar{I}_0 \\
&+\bar{\phi}_9^2\bar{I}_0-\bar{\phi}_5\bar{\phi}_9^2\bar{I}_0+\bar{\phi}_1^2(1+\bar{\phi}_7)(\bar{\phi}_4+(-1+\bar{\phi}_5)\bar{I}_0) \\
&-\bar{\phi}_2(1+\bar{\phi}_7)(\bar{\phi}_4+(-1+\bar{\phi}_5)\bar{I}_0)^2-\bar{\phi}_1(1+\bar{\phi}_7)(-3\bar{\phi}_6+3\bar{\phi}_5\bar{\phi}_6 \\
&-3\bar{\phi}_6\bar{\phi}_7+3\bar{\phi}_5\bar{\phi}_6\bar{\phi}_7+\bar{\phi}_3(-1+\bar{\phi}_5)(1+\bar{\phi}_7)-\bar{\phi}_4\bar{\phi}_8-2\bar{\phi}_8\bar{I}_0 \\
&+2\bar{\phi}_5\bar{\phi}_8\bar{I}_0-p_2(\bar{\phi}_4+(-1+\bar{\phi}_5)\bar{I}_0)))+\bar{G}_0(p_2\bar{\phi}_4\bar{\phi}_6\bar{\phi}_8+\bar{\phi}_6^2\bar{\phi}_8 \\
&-\bar{\phi}_5\bar{\phi}_6^2\bar{\phi}_8+p_2\bar{\phi}_4\bar{\phi}_6\bar{\phi}_7\bar{\phi}_8+2\bar{\phi}_6^2\bar{\phi}_7\bar{\phi}_8-2\bar{\phi}_5\bar{\phi}_6^2\bar{\phi}_7\bar{\phi}_8+\bar{\phi}_6^2\bar{\phi}_7^2\bar{\phi}_8 \\
&-\bar{\phi}_5\bar{\phi}_6^2\bar{\phi}_7^2\bar{\phi}_8+\bar{\phi}_4\bar{\phi}_6\bar{\phi}_8^2+\bar{\phi}_4\bar{\phi}_6\bar{\phi}_7\bar{\phi}_8^2+p_2\bar{\phi}_4\bar{\phi}_6\bar{\phi}_9+\bar{\phi}_6^2\bar{\phi}_9 \\
&-\bar{\phi}_5\bar{\phi}_6^2\bar{\phi}_9+\bar{\phi}_6^2\bar{\phi}_7\bar{\phi}_9-\bar{\phi}_5\bar{\phi}_6^2\bar{\phi}_7\bar{\phi}_9+\bar{\phi}_4\bar{\phi}_6\bar{\phi}_8\bar{\phi}_9+\bar{\phi}_4\bar{\phi}_6\bar{\phi}_9^2 \\
&-p_2\bar{\phi}_6\bar{\phi}_8\bar{I}_0+p_2\bar{\phi}_5\bar{\phi}_6\bar{\phi}_8\bar{I}_0-p_2\bar{\phi}_6\bar{\phi}_7\bar{\phi}_8\bar{I}_0+p_2\bar{\phi}_5\bar{\phi}_6\bar{\phi}_7\bar{\phi}_8\bar{I}_0 \\
&+p_2\bar{\phi}_4\bar{\phi}_8^2\bar{I}_0+\bar{\phi}_6\bar{\phi}_8^2\bar{I}_0-\bar{\phi}_5\bar{\phi}_6\bar{\phi}_8^2\bar{I}_0+\bar{\phi}_6\bar{\phi}_7\bar{\phi}_8^2\bar{I}_0-\bar{\phi}_5\bar{\phi}_6\bar{\phi}_7\bar{\phi}_8^2\bar{I}_0
\end{aligned}
\tag{8.83}
$$

$$
\begin{aligned}
&+ \bar{\phi}_4\bar{\phi}_8^3\bar{I}_0 - p_2\bar{\phi}_6\bar{\phi}_9\bar{I}_0 + p_2\bar{\phi}_5\bar{\phi}_6\bar{\phi}_9\bar{I}_0 - \bar{\phi}_6\bar{\phi}_9^2\bar{I}_0 + \bar{\phi}_5\bar{\phi}_6\bar{\phi}_9^2\bar{I}_0 \\
&- p_2\bar{\phi}_8^2\bar{I}_0 + p_2\bar{\phi}_5\bar{\phi}_8^2\bar{I}_0^2 - 3\bar{\phi}_1^2\bar{\phi}_3(1+\bar{\phi}_7)(\bar{\phi}_4 + (-1+\bar{\phi}_5)\bar{I}_0) \\
&- \bar{\phi}_1(-\bar{\phi}_3(1+\bar{\phi}_7)(3(-1+\bar{\phi}_5)\bar{\phi}_6(1+\bar{\phi}_7) - \bar{\phi}_8(\bar{\phi}_4 \\
&- 2(-1+\bar{\phi}_5)\bar{I}_0)) + p_2(\bar{\phi}_4 + (-1+\bar{\phi}_5)\bar{I}_0)(\bar{\phi}_3(1+\bar{\phi}_7) \\
&+ 2(\bar{\phi}_6 + \bar{\phi}_6\bar{\phi}_7 + \bar{\phi}_8\bar{I}_0)) + 2(-(-1+\bar{\phi}_5)\bar{\phi}_6^2(1+\bar{\phi}_7)^2 + \bar{\phi}_4\bar{\phi}_8^2\bar{I}_0 \\
&+ \bar{\phi}_6(\bar{\phi}_4(\bar{\phi}_8 + \bar{\phi}_7\bar{\phi}_8 + \bar{\phi}_9) - (-1+\bar{\phi}_5)(\bar{\phi}_8 + \bar{\phi}_7\bar{\phi}_8 - \bar{\phi}_9)\bar{I}_0)))) / \\
&(p_2\bar{\phi}_4\bar{\phi}_6\bar{\phi}_8 + \bar{\phi}_6^2\bar{\phi}_8 - \bar{\phi}_5\bar{\phi}_6^2\bar{\phi}_8 + p_2\bar{\phi}_4\bar{\phi}_6\bar{\phi}_6\bar{\phi}_7\bar{\phi}_8 + 2\bar{\phi}_6^2\bar{\phi}_7\bar{\phi}_8 \\
&- 2\bar{\phi}_5\bar{\phi}_6^2\bar{\phi}_7\bar{\phi}_8 + \bar{\phi}_6^2\bar{\phi}_7^2\bar{\phi}_8 - \bar{\phi}_5\bar{\phi}_6^2\bar{\phi}_7^2\bar{\phi}_8 + \bar{\phi}_4\bar{\phi}_6\bar{\phi}_8^2 + \bar{\phi}_4\bar{\phi}_6\bar{\phi}_7\bar{\phi}_8^2 \\
&+ p_2\bar{\phi}_4\bar{\phi}_6\bar{\phi}_9 + \bar{\phi}_6^2\bar{\phi}_9 - \bar{\phi}_5\bar{\phi}_6^2\bar{\phi}_9 + \bar{\phi}_6^2\bar{\phi}_7\bar{\phi}_9 - \bar{\phi}_5\bar{\phi}_6^2\bar{\phi}_9 + \bar{\phi}_4\bar{\phi}_6\bar{\phi}_8\bar{\phi}_9 \\
&+ \bar{\phi}_4\bar{\phi}_6\bar{\phi}_9^2 - \bar{G}_0^2(-1+\bar{\phi}_5)(1+\bar{\phi}_7)(\bar{\phi}_1 + \bar{\phi}_1\bar{\phi}_7 + \bar{\phi}_8 + \bar{\phi}_7\bar{\phi}_8 + \bar{\phi}_9) \\
&- p_2\bar{\phi}_6\bar{\phi}_8\bar{I}_0 + p_2\bar{\phi}_5\bar{\phi}_6\bar{\phi}_8\bar{I}_0 - p_2\bar{\phi}_6\bar{\phi}_7\bar{\phi}_8\bar{I}_0 + p_2\bar{\phi}_5\bar{\phi}_6\bar{\phi}_7\bar{\phi}_8\bar{I}_0 \\
&+ p_2\bar{\phi}_4\bar{\phi}_8^2\bar{I}_0 + \bar{\phi}_6\bar{\phi}_8^2\bar{I}_0 - \bar{\phi}_5\bar{\phi}_6\bar{\phi}_8^2 + \bar{\phi}_6\bar{\phi}_7\bar{\phi}_8^2\bar{I}_0 - \bar{\phi}_5\bar{\phi}_6\bar{\phi}_7\bar{\phi}_8^2\bar{I}_0 \\
&+ \bar{\phi}_4\bar{\phi}_8^3\bar{I}_0 - p_2\bar{\phi}_6\bar{\phi}_9\bar{I}_0 + p_2\bar{\phi}_5\bar{\phi}_6\bar{\phi}_9\bar{I}_0 - \bar{\phi}_6\bar{\phi}_9^2\bar{I}_0 + \bar{\phi}_5\bar{\phi}_6\bar{\phi}_9^2\bar{I}_0 \\
&- p_2\bar{\phi}_8^2\bar{I}_0^2 + p_2\bar{\phi}_5\bar{\phi}_8^2\bar{I}_0^2 + \bar{\phi}_1^2\bar{\phi}_3(1+\bar{\phi}_7)(\bar{\phi}_4 + (-1+\bar{\phi}_5)\bar{I}_0) \\
&+ \bar{\phi}_1\bar{\phi}_3(-(-1+\bar{\phi}_5)\bar{\phi}_6(1+\bar{\phi}_7)^2 + \bar{\phi}_4\bar{\phi}_8 + \bar{\phi}_4\bar{\phi}_7\bar{\phi}_8 \\
&+ 2\bar{\phi}_4\bar{\phi}_9 - 2\bar{\phi}_9\bar{I}_0 + 2\bar{\phi}_5\bar{\phi}_9\bar{I}_0 + p_2(1+\bar{\phi}_7)(\bar{\phi}_4 + (-1+\bar{\phi}_5)\bar{I}_0)) \\
&- \bar{G}_0(p_2\bar{\phi}_4\bar{\phi}_8 + 2\bar{\phi}_6\bar{\phi}_8 - 2\bar{\phi}_5\bar{\phi}_6\bar{\phi}_8 + p_2\bar{\phi}_4\bar{\phi}_7\bar{\phi}_8 + 4\bar{\phi}_6\bar{\phi}_7\bar{\phi}_8 \\
&- 2\bar{\phi}_5\bar{\phi}_6\bar{\phi}_7\bar{\phi}_8 + 2\bar{\phi}_6\bar{\phi}_7^2\bar{\phi}_8 - 2\bar{\phi}_5\bar{\phi}_6\bar{\phi}_7^2\bar{\phi}_8 + \bar{\phi}_4\bar{\phi}_8^2 + \bar{\phi}_4\bar{\phi}_7\bar{\phi}_8^2 \\
&+ p_2\bar{\phi}_4\bar{\phi}_9 + 2\bar{\phi}_6\bar{\phi}_9 - 2\bar{\phi}_5\bar{\phi}_6\bar{\phi}_9 + 2\bar{\phi}_6\bar{\phi}_7\bar{\phi}_9 - 2\bar{\phi}_5\bar{\phi}_6\bar{\phi}_7\bar{\phi}_9 \\
&+ \bar{\phi}_4\bar{\phi}_8\bar{\phi}_9 + \bar{\phi}_4\bar{\phi}_9^2 - p_2\bar{\phi}_8\bar{I}_0 + p_2\bar{\phi}_5\bar{\phi}_8\bar{I}_0 - p_2\bar{\phi}_5\bar{\phi}_7\bar{\phi}_8\bar{I}_0
\end{aligned}
$$

$$
\begin{aligned}
&+ \bar{\phi}_8^2\bar{I}_0 - \bar{\phi}_5\bar{\phi}_8^2\bar{I}_0 + \bar{\phi}_7\bar{\phi}_8^2\bar{I}_0 - \bar{\phi}_5\bar{\phi}_7\bar{\phi}_8^2\bar{I}_0 - p_2\bar{\phi}_9\bar{I}_0 + p_2\bar{\phi}_5\bar{\phi}_9\bar{I}_0 \\
&- \bar{\phi}_9^2\bar{I}_0 + \bar{\phi}_5\bar{\phi}_9^2\bar{I}_0 + \bar{\phi}_1^2(1+\bar{\phi}_7)(\bar{\phi}_4 + (-1+\bar{\phi}_5)\bar{I}_0) \\
&+ \bar{\phi}_2(1+\bar{\phi}_7)(\bar{\phi}_4 + (-1+\bar{\phi}_5)\bar{I}_0)^2 + \bar{\phi}_1(\bar{\phi}_6 - \bar{\phi}_5\bar{\phi}_6 + 2\bar{\phi}_6\bar{\phi}_7 \\
&- 2\bar{\phi}_5\bar{\phi}_6\bar{\phi}_7 + \bar{\phi}_6\bar{\phi}_7^2 - \bar{\phi}_5\bar{\phi}_6\bar{\phi}_7^2 - \bar{\phi}_3(-1+\bar{\phi}_5)(1+\bar{\phi}_7)^2 \\
&+ \bar{\phi}_4\bar{\phi}_8 + \bar{\phi}_4\bar{\phi}_7\bar{\phi}_8 + 2\bar{\phi}_4\bar{\phi}_9 - 2\bar{\phi}_9\bar{I}_0 + 2\bar{\phi}_5\bar{\phi}_9\bar{I}_0 \\
&+ p_2(1+\bar{\phi}_7)(\bar{\phi}_4 + (-1+\bar{\phi}_5)\bar{I}_0)))).
\end{aligned}
$$

The fifth coefficients of the Taylor Series expansions and their evaluations at $t = 0$ are given by

$$
\begin{aligned}
y_1^{(4)}(0) =& -2\dot{y}_1(0)(-p_2p_3(-I_b+I_0) + p_3\dot{y}_2(0)) - 3p_3(-I_b+I_0)\ddot{y}_1(0) \qquad (8.84)\\
&- G_0(-p_2(-p_2p_3(-I_b+I_0) + p_3\dot{y}_2(0)) + p_3\ddot{y}_2(0)) - p_2\dddot{y}_1(0) \\
y_2^{(4)}(0) =& 3p_4\ddot{y}_1(0) - p_6\dddot{y}_2(0) \qquad (8.85)\\
\tilde{y}_1^{(4)}(0) =& -3\tilde{\phi}_2\dot{\tilde{y}}_1(0)(\dot{\tilde{y}}_2(0) - \tilde{\phi}_5\dot{\tilde{y}}_2(0)) - 3\tilde{\phi}_1(-\tilde{\phi}_4 + \tilde{I}_0 - \tilde{\phi}_5\tilde{I}_0)\ddot{\tilde{y}}_1(0) \qquad (8.86)\\
&- \tilde{G}_0\tilde{\phi}_2(\ddot{\tilde{y}}_2(0)) - \tilde{\phi}_5\ddot{\tilde{y}}_2(0) - \tilde{\phi}_1\dddot{\tilde{y}}_1(0) \\
\tilde{y}_2^{(4)}(0) =& -(\tilde{G}_0 - \tilde{\phi}_6)\tilde{\phi}_9^3 + 3\tilde{\phi}_9^2\dot{\tilde{y}}_1(0) - 3\tilde{\phi}_9^2\ddot{\tilde{y}}_1(0) + \dddot{\tilde{y}}_1(0) + \tilde{\phi}_7\dddot{\tilde{y}}_1(0) \qquad (8.87)\\
&- \tilde{\phi}_8\dddot{\tilde{y}}_2(0).
\end{aligned}
$$

As $y_1^{(4)}(0) = \tilde{y}_1^{(4)}(0)$, equating RHS of (8.84) and (8.86) after substituting in (8.62), (8.63), (8.69), (8.71), (8.76), (8.77), (8.82) and (8.83) gives

$$p_2 = 0. \qquad (8.88)$$

Since generically $p_2 \neq 0$ this provides a contradiction, hence the outputs for the EMM and CLMM are not consistent and the two models are therefore distinguishable over the pre-switching phase.

Therefore, the CLMM and the EMM are structural distinguishable from each other.

Chapter 9

Conclusions

Presented in this thesis are structural identifiability analyses successfully performed for the first time on an important set of glucose-insulin dynamics models, also demonstrating the importance of these analyses. The results obtained here have generated significant information which will allow diabetes-related research communities to gain further insight into these glucose-insulin models and to undertake model-based studies and parameter estimation with greater confidence.

This thesis demonstrates the structural identifiability of several glucose-insulin dynamics models, including two versions of the well-cited Minimal Model, a Euglycemic Hyperinsulinemic Clamp (EIC) model, and two modified versions of the Minimal Model: Closed-Loop Minimal Model (CLMM) and Double-Pole in Closed-Loop Minimal Model (DPCLMM). As far as the author is aware, this is the first time that structural identifiability (*a priori*) analyses of these models (with these specific model structures) has been performed.

This thesis presents structural identifiability analyses of the original form of the Minimal Model (OMM) and over the two phases of the Extended Minimal Model (EMM) (pre- and post- switching phases). The analysis using

the Taylor Series approach [Pohjanpalo, 1978] shows that the OMM is structurally unidentifiable as the parameter p_2 (the rate constant which explains the ability of the spontaneous decrease of tissue glucose uptake) is unidentifiable, as further information for insulin concentration ($\dot{I}(t)$) is required to determine the uniqueness of the parameter p_2. Therefore, using the OMM alone, and parameter estimation commonly followed in practice using this model version, users are at risk of calculating insulin sensitivity incorrectly or inaccurately (since $S_I = p_3/p_2$), which is one of the main purposes of application of the OMM. Bergman et al. [1979] showed that the OMM is numerically identifiable. However, the results obtained in this thesis demonstrate that a numerically identifiable model is not necessarily structurally globally identifiable.

The structural identifiability analysis performed on the EMM over the post-switching phase is performed using the Taylor Series approach [Pohjanpalo, 1978]. The results show that the EMM over the pre-switching phase is structurally globally identifiable, if the basal level of glucose concentration above is known. For the structural identifiability analysis of the EMM over the pre-switching phase, the Taylor Series approach [Pohjanpalo, 1978] was first used and no conclusive results could be drawn from the analysis using this approach (due to the fact that this approach is only necessary but not sufficient). The analysis was subsequently carried out using a more recent form of the Similarity Transformation approach for autonomous systems [Evans et al., 2002] and the results showed that the model is in fact structurally globally identifiable and that all parameters are uniquely identifiable for observation of glucose and insulin from an IVGTT experiment.

Parameter estimation for the EMM is usually performed in two steps (for details see Chapter 2, Section 2.4). In this thesis, the parameter estimation is performed simultaneously by combining the pre- and post- switching phases of the insulin system equation using appropriate sign functions (see Chapter

4, Section 4.6). Fits were performed using IVGTT data sets from different subjects. The statistical information obtained within FACSIMILE shows that parameter estimates for p_2 and p_3 (key parameters for defining insulin sensitivity) have high values of Standard Deviation for the Log-Normal (SLDN) distribution (i.e. approximate percentage errors) generated within FACSIMILE. Other fits performed show that the parameters p_2 and p_3 are not always determinable. This demonstrates that the EMM may also not be wholly appropriate for determining insulin sensitivity (S_I), as the parameters p_2 and p_3 are at risk of being undeterminable through parameter estimation using the EMM. This also demonstrates that a globally identifiable model does not guarantee good parameter fitting and numerical identifiabilility.

The Euglycemic Hyperinsulinemic Clamp (EIC) model [Picchini et al., 2005] was the first mathematical model (as far as this author is aware) that was developed to accurately describe an EIC experiment. This model allows users to understand and generate more information on the EIC process, which may or may not be obtainable during an experiment. The structural identifiability analysis for the EIC model is performed using the Taylor Series approach. The result shows that the EIC model is structurally globally identifiable under the conditions that the volume parameters V_g and V_i are known; commonly in practice values for these parameters can be determined separately.

Parameter estimation was performed using the EIC model on glucose clamp data. The results show that the EIC model is able to generate a reasonable glucose dynamics response for the glucose clamp. However, the EIC model does not generate the corresponding insulin dynamics response well, most probably due to the fact that the EIC model was designed to generate a steady state insulin response for an EIC experiment.

As the EIC model does not fit the insulin dynamics response of the glucose clamp, this may be the reason for high Residual Sum of Squares (RSS)

values for the fits obtained. All other fits performed (see Appendix B) show that the EIC model can only be used for more accurately fitting the glucose dynamics response alone.

The Closed-Loop Minimal Model (CLMM) is a recent modified version of the MM. Unlike the MM, the CLMM is able to generate a complete course of IVGTT experiment (i.e. first and second phases of glucose and insulin responses) [Arundel et al., 2010]. A structural identifiability analysis of the CLMM was also carried out using a version of the Similarity Transformation approach [Evans et al., 2002]. The results obtained show that the CLMM is structural unidentifiable. A reparameterisation procedure was subsequently carried out and through regrouping the initial system parameters appropriately, the model parameters were reduced from 11 to 9 parameters. The structural identifiability of the reparameterised CLMM was performed using a more recent version of the Similarity Transformation approach [Evans et al., 2002] and the result shows that the reparameterised CLMM is actually structurally globally identifiable under the condition that the basal level of glucose is known.

Parameter estimation was performed using the reparameterised CLMM with IVGTT data containing first and second phase glucose-insulin dynamics responses. This shows that the repameterised CLMM is able to generate a reasonable first phase response of glucose-insulin dynamics.

A structural indistinguishability analysis was also performed and has shown that the CLMM is distinguishable from the EMM at both pre- and post- switching phases given the same observations of glucose and insulin concentrations.

The structural identifiability analysis for the DPCLMM using the Taylor Series approach was not applicable due to the complex structures of the model. A structural identifiability analysis using the Similarity Transforma-

tion approach was then considered. However, the DPCLMM does not satisfy the Observability Rank Criterion. Therefore, there is as yet no conclusive result for the structural identifiability of the DPCLMM.

This thesis demonstrates the structural identifiability analyses of the OMM and EMM for the first time, since these models were published in 1979 and 1981 respectively [Bergman et al., 1979; Bergman and Bowden, 1981] and for the specific model structures considered. The analyses for the MM demonstrate certain issues including the fact that the MM may not be appropriate for calculating insulin sensitivity or modelling the glucose and insulin dynamics for IVGTT experiments.

9.1 Suggestions for Future Work

The parameter estimation performed using the EIC model demonstrates that this model is able to reasonably generate only the glucose dynamics response for a glucose clamp. Therefore, the glucose clamp model needs to be developed further including slight modification of the EIC model, to also generate appropriate transient insulin responses.

The parameter estimation for the CLMM has demonstrated that (unlike the OMM and EMM), the model is able to generate first and second phase responses for glucose-insulin dynamics responses. However, tighter fits are required with much lower RSS values and lower SDLN values, where all the parameters are well determined. The parameter estimates for IVGTT data for other subjects is also highly desired for further study of the CLMM. This also suggests that the CLMM may yield more appropriate and accurate ways of calculating insulin sensitivity using IVGTT data than other previously published models.

The DPCLMM is a model highly recommended by its authors Arundel

et al. [2010]. Like the CLMM, it also captures the complete process of an IVGTT including both the first and second phases of glucose-insulin dynamics responses. Therefore, it is important to determine the *a priori* identifiability of the DPCLMM. If the model can be proven to be structurally globally identifiable or a necessary reparameterisation performed, then parameter estimation of the DPCLMM with respect to IVGTT data may also yield more appropriate and accurate means of determining insulin sensitivity S_I.

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Appendix A

Parameter Estimates for EMM

This section includes the parameter estimation results for the Extended Minimal Model (EMM) as outlined in Chapter 4.

	Fit 1		Fit 2	
Parameters	Value	[SDLN]	Value	[SDLN]
p_1	$2.264 \cdot 10^{-2}$	[0.558]	$3.072 \cdot 10^{-2}$	[0.493]
p_2	$2.351 \cdot 10^{-1}$	[0.780]	$1.112 \cdot 10^{-1}$	[0.718]
p_3	$1.060 \cdot 10^{-4}$	[0.729]	$4.518 \cdot 10^{-5}$	[1.295]
p_4	$9.024 \cdot 10^{-3}$	[1.403]	$1.206 \cdot 10^{-2}$	[0.338]
p_5	8.265	[0.262]	6.395	[0.106]
p_6	$9.756 \cdot 10^{-2}$	[0.121]	$1.148 \cdot 10^{-1}$	[0.065]
	RSS=6.326		RSS=$1.229 \cdot 10$	

Table A.1: The Values and SDLNs for Fits 1 and 2 (Subject 3).

	Fit 4		Fit 6	
Parameters	Value	[SDLN]	Value	[SDLN]
p_1	$1.728 \cdot 10^{-2}$	[0.472]	$2.349 \cdot 10^{-2}$	[0.039]
p_2	$5.173 \cdot 10^{-2}$	[1.114]	-	-
p_3	$1.817 \cdot 10^{-5}$	[1.844]	-	-
p_4	$9.838 \cdot 10^{-3}$	[0.144]	$1.038 \cdot 10^{-2}$	[0.138]
p_5	5.946	[0.049]	6.175	[0.037]
p_6	$1.033 \cdot 10^{-1}$	[0.051]	$1.041 \cdot 10^{-1}$	[0.051]
	RSS=3.3173		RSS=3.7108	

Table A.2: Value and SDLNs for Fits 5 and 6 (Subject 8)

	Fit 7		Fit 8	
Parameters	Value	[SDLN]	Value	[SDLN]
p_1	$1.121 \cdot 10^{-2}$	[0.860]	$2.202 \cdot 10^{-2}$	[0.076]
p_2	$6.194 \cdot 10^{-2}$	[0.569]	-	-
p_3	$7.536 \cdot 10^{-5}$	[0.855]	$1.709 \cdot 10^{-5}$	[0.167]
p_4	$1.926 \cdot 10^{-2}$	[0.087]	$1.731 \cdot 10^{-2}$	[0.118]
p_5	6.803	[0.030]	6.782	[0.048]
p_6	$1.825 \cdot 10^{-1}$	[0.039]	$1.719 \cdot 10^{-1}$	[0.039]
	RSS= 1.3691		RSS=1.6247	

Table A.3: Value and SDLNs for Fits 7 and 8 (Subject 17).

	Fit 1 (Subject 3)					
Row/Column	p_1	p_2	p_3	p_4	p_5	p_6
p_1	1.000	-0.509	-0.941	-0.090	0	-0.095
p_2	-0.509	1.000	0.758	0.169	0.116	0.062
p_3	-0.941	0.758	1.000	0.139	0.021	0.112
p_4	-0.090	0.169	0.139	1.000	0.657	0.744
p_5	0	0.116	0.021	0.657	1.000	0.245
p_6	-0.095	0.062	0.112	0.744	0.245	1.000
	Fit 2 (Subject 3)					
Row/Column	p_1	p_2	p_3	p_4	p_5	p_6
p_1	1.000	0.348	-0.522	0.004	0.118	-0.039
p_2	0.348	1.000	0.602	0.029	-0.012	-0.019
p_3	-0.522	0.602	1.000	0.033	-0.126	0.047
p_4	0.004	0.029	0.033	1.000	0.782	0.823
p_5	0.118	-0.012	-0.126	0.782	1.000	0.421
p_6	-0.039	-0.019	0.047	0.823	0.421	1.000

Table A.4: Correlation matrix of the well-determined parameters for Fits 1 and 2 (Subject 3) for the EMM.

	Fit 4 (Subject 8)					
Row/Column	p_1	p_2	p_3	p_4	p_5	p_6
p_1	1.000	-0.851	-0.978	0.02	0.234	-0.116
p_2	-0.851	1.000	0.935	0.225	0.022	0.187
p_3	-0.978	0.935	1.000	0.066	-0.188	0.154
p_4	0.02	0.225	0.066	1.000	0.552	0.735
p_5	0.234	0.022	-0.188	0.552	1.000	0.114
p_6	-0.116	0.187	0.154	0.735	0.114	1.000
	Fit 6 (Subject 8)					
Row/column	p_1	p_4	p_5	p_6		
p_1	1.000	0.059	-0.593	0.027		
p_4	0.059	1.000	0.117	0.767		
p_5	-0.593	0.117	1.000	0.454		
p_6	0.027	0.767	0.454	1.000		

Table A.5: Correlation matrix of the well-determined parameters for Fits 4 and 6 (Subject 8) for the EMM.

	Fit 7 (Subject 17)					
Row/Column	p_1	p_2	p_3	p_4	p_5	p_6
p_1	1.000	-0.937	-0.988	0.247	0.46	-0.058
p_2	-0.937	1.000	0.976	-0.064	-0.379	0.131
p_3	-0.988	0.976	1.000	-0.179	-0.458	0.103
p_4	0.247	-0.064	-0.179	1.000	0.539	0.634
p_5	0.46	-0.379	-0.458	0.539	1.000	-0.012
p_6	-0.058	0.131	0.103	0.634	-0.012	1.000
	Fit 8 (Subject 17)					
Row/column	p_1	p_3	p_4	p_5	p_6	
p_1	1.000	-0.832	0.196	-0.087	0.110	
p_3	-0.832	1.000	-0.238	-0.122	-0.027	
p_4	0.196	-0.238	1.000	0.725	0.527	
p_5	-0.087	-0.122	0.725	1.000	0.016	
p_6	0.110	-0.027	0.527	0.016	1.000	

Table A.6: Correlation matrix of well-determined parameters for Fits 7 and 8 (Subject 17) for the EMM.

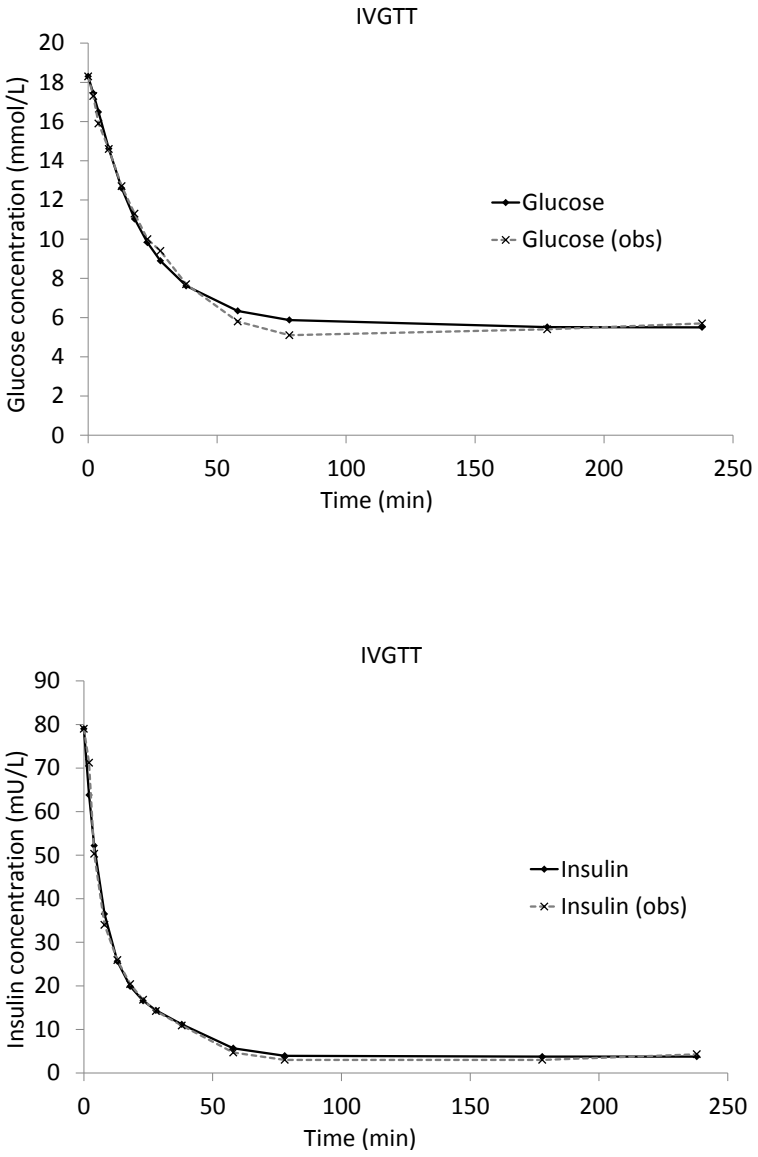

Figure A.1: Glucose and insulin responses for the EMM, Fit 1 (Subject 3).

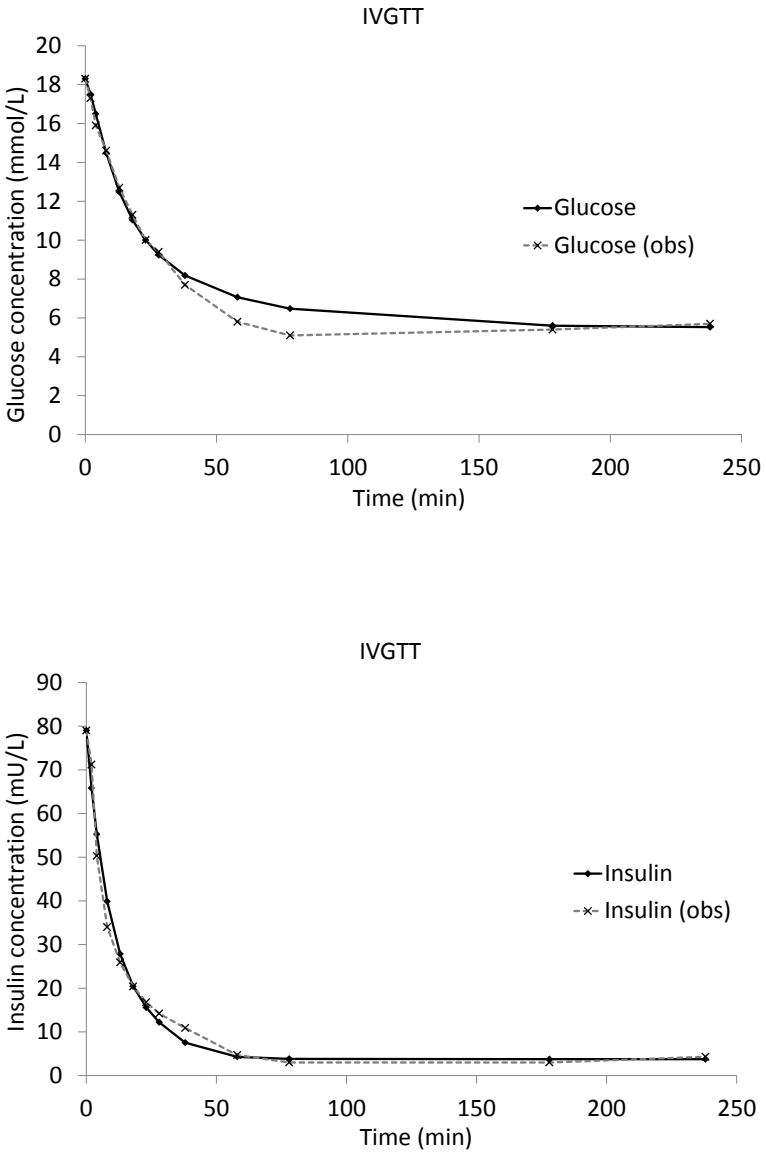

Figure A.2: Glucose and insulin responses for the EMM, Fit 2 (Subject 3).

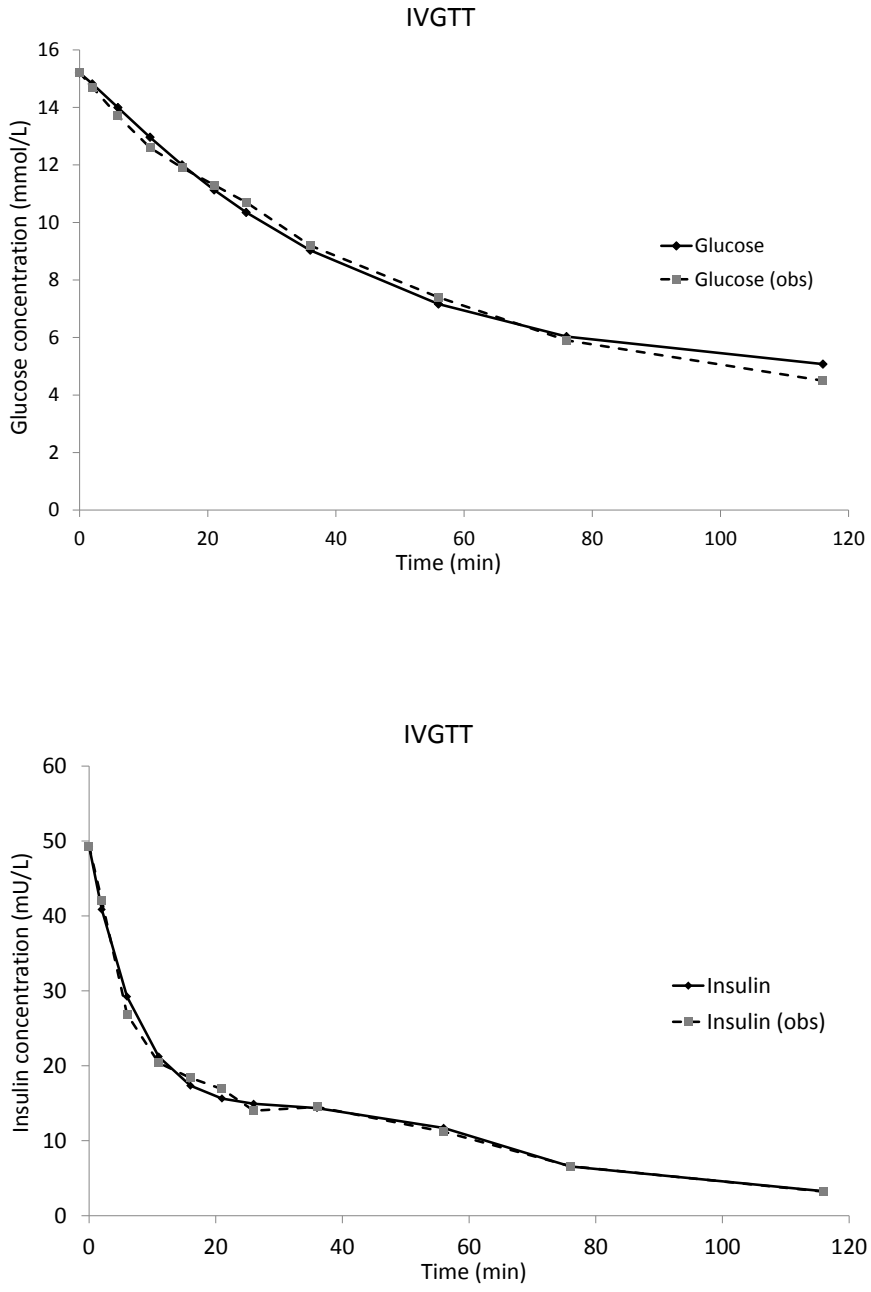

Figure A.3: Glucose and insulin responses for the EMM, Fit 4 (Subject 8).

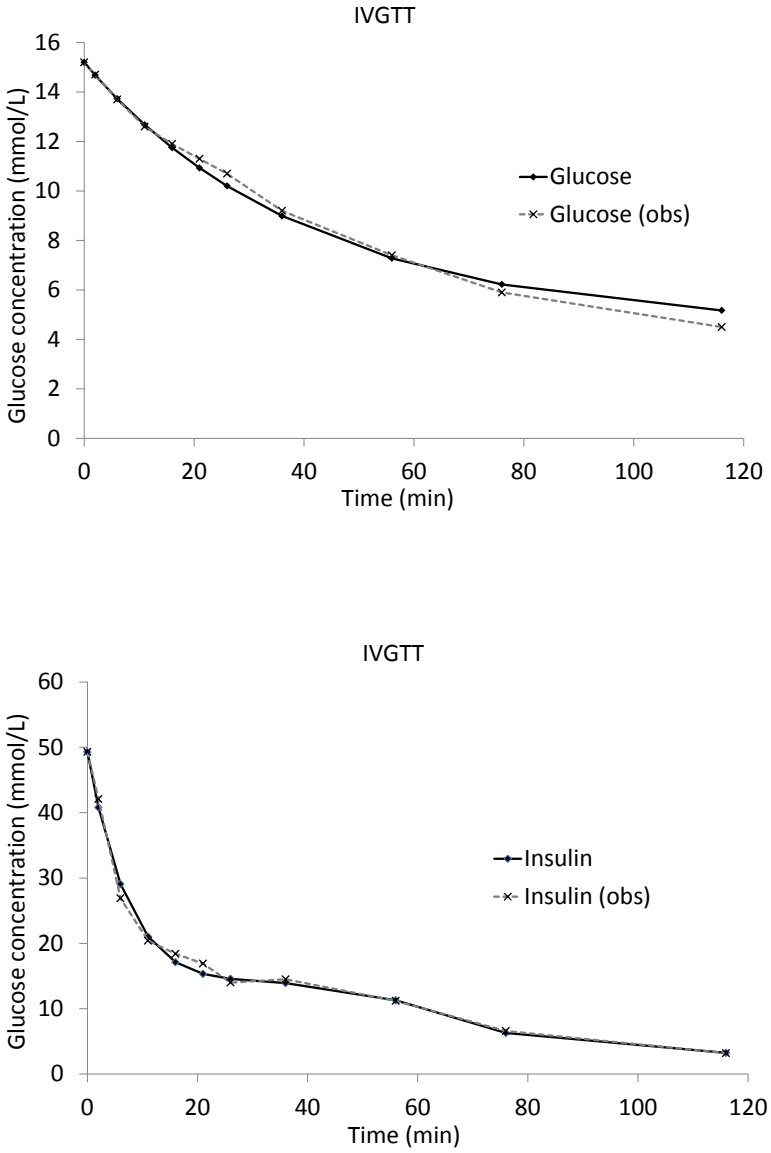

Figure A.4: Glucose and insulin responses for the EMM, Fit 6 (Subject 8).

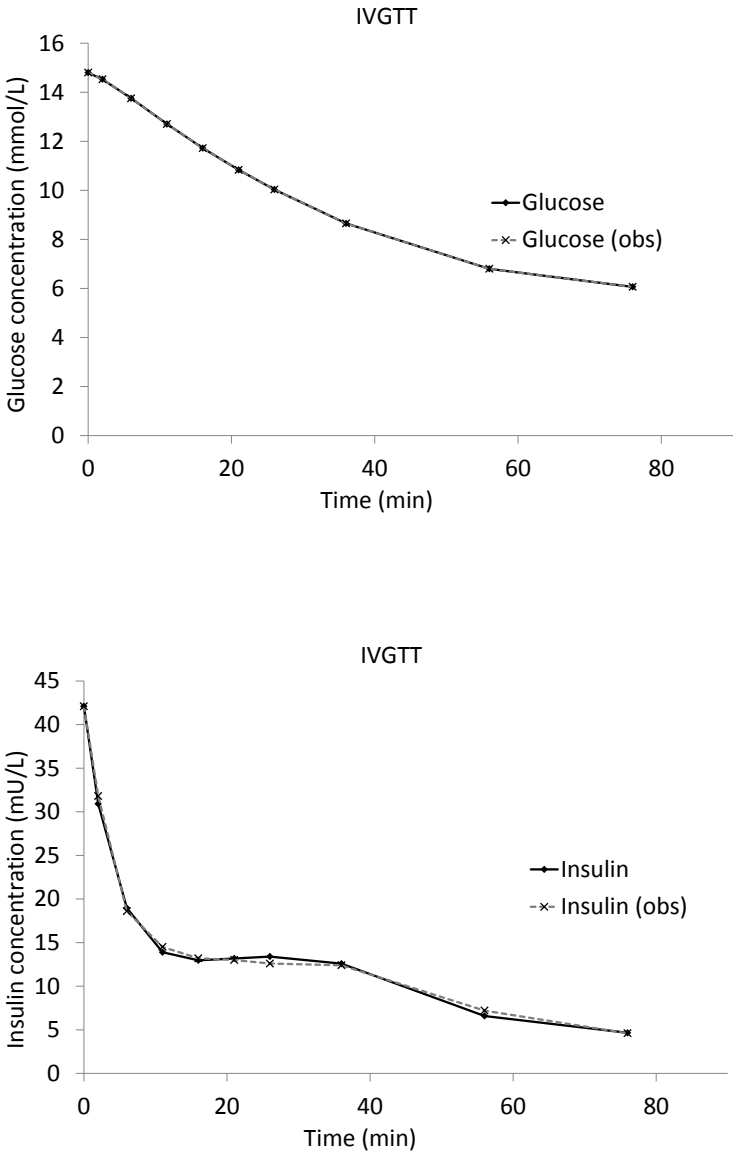

Figure A.5: Glucose and insulin responses for the EMM, Fit 7 (Subject 17).

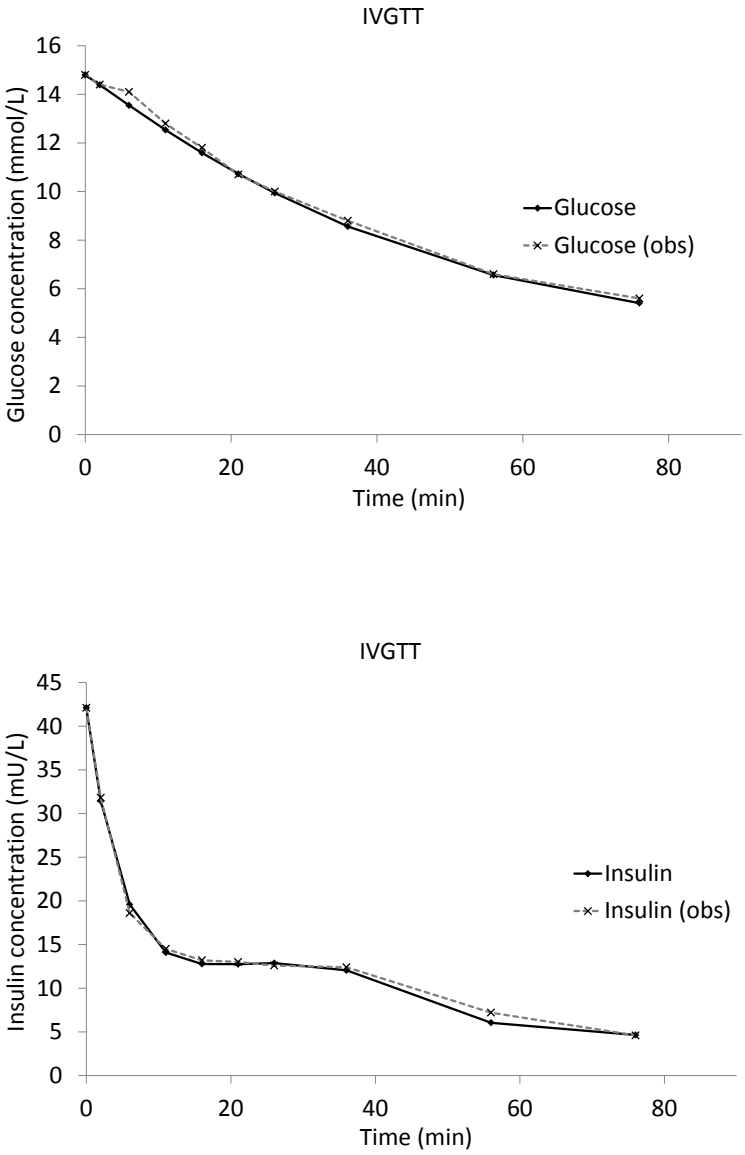

Figure A.6: Glucose and insulin responses for the EMM, Fit 8 (Subject 17).

Appendix B

Parameter Estimates for Euglycemic Hyperinsulinemic Clamp Model

This section includes the parameter estimation results for the EIC Model as outlined in Chapter 5.

	Fit 2		Fit 3		Fit 4	
	Value	[SDLN]	Value	[SDLN]	Value	[SDLN]
V_g	-	-	$1.055 \cdot 10^{-3}$	[0.474]	$4.661 \cdot 10^{-3}$	[1.549]
V_i	$1.040 \cdot 10^{-1}$	[1.386]	-	-	$7.301 \cdot 10^{-2}$	[0.391]
K_{xgI}	$3.584 \cdot 10^{1}$	[1.644]	6.467	[0.352]	-	-
K_{xi}	$5.406 \cdot 10^{-2}$	[1.394]	$3.826 \cdot 10^{-2}$	[0.564]	-	-
T_{ghmax}	$5.406 \cdot 10^{-2}$	[0.716]	9.619	[0.824]	$5.589 \cdot 10^{2}$	[1.283]
T_{iG}	-	-	-	-	-	-
λ	$8.497 \cdot 10^{-3}$	[1.139]	$1.165 \cdot 10^{-2}$	[0.540]	$9.886 \cdot 10^{-3}$	[1.167]
	RSS=$2.267 \cdot 10^{2}$		RSS=$2.252 \cdot 10^{2}$		RSS=$2.259 \cdot 10^{2}$	

Table B.1: Values and SDLNs for Fits 2, 3 and 4 (Subject 3).

	Fit 5		Fit 6	
Parameters	Value	[SDLN]	Value	[SDLN]
V_g	$1.408 \cdot 10^{-4}$	[0.425]	$6.000 \cdot 10^{-2}$	[0.870]
V_i	3.417	[0.459]	$1.578 \cdot 10$	[0.654]
K_{xgI}	$1.107 \cdot 10^{2}$	[0.612]	$1.771 \cdot 10^{-1}$	[0.884]
K_{xi}	$2.142 \cdot 10^{-2}$	[0.232]	-	-
T_{ghmax}	3.417	[0.459]	$1.030 \cdot 10^{3}$	[1.076]
T_{iG}	$6.431 \cdot 10^{-2}$	[0.410]	6.546	[0.650]
λ	-	-	$2.820 \cdot 10^{-2}$	[0.223]
	RSS=$4.024 \cdot 10^{2}$		RSS=$4.017 \cdot 10^{2}$	

Table B.2: Values and SDLNs for Fits 5 and 6 (Subject 8).

	Fit 8		Fit 9	
Parameters	Value	[SLDN]	Value	[SDLN]
V_g	-	-	$4.430 \cdot 10^{-2}$	[1.404]
V_i	$3.697 \cdot 10^{-1}$	[0.575]	$2.181 \cdot 10^{-1}$	[0.331]
K_{xgI}	$2.454 \cdot 10^{-1}$	[0.659]	$1.343 \cdot 10^{-1}$	[0.844]
K_{xi}	$4.841 \cdot 10^{-2}$	[0.294]	-	-
T_{ghmax}	$2.191 \cdot 10^{2}$	[0.785]	$1.201 \cdot 10$	[0.615]
T_{iG}	$1.181 \cdot 10^{-1}$	[0.501]	$8.685 \cdot 10^{-2}$	[0.327]
λ	$5.619 \cdot 10^{-2}$	[0.072]	$1.522 \cdot 10^{-2}$	[0.700]
	RSS=$1.669 \cdot 10^{2}$		RSS=$1.687 \cdot 10^{2}$	

Table B.3: Values and SDLNs for Fits 8 and 9 (Subject 17).

	Fit 2 (Subject 3)				
Row / Column	V_i	K_{xgI}	T_{ghmax}	K_{xi}	λ
V_i	1.000	0.848	0.251	-0.999	-0.695
K_{xgI}	0.848	1.000	0.085	-0.844	-0.906
T_{ghmax}	0.251	0.085	1.000	-0.245	0.337
K_{xi}	-0.999	-0.844	-0.245	1.000	0.694
λ	-0.695	-0.906	0.337	0.694	1.000

	Fit 3 (Subject 3)					
Row/Column	V_g	K_{xgI}	T_{iG}	K_{xi}	λ	T_{ghmax}
V_g	1.000	0.175	0.241	0.228	-0.832	-0.492
K_{xgI}	0.175	1.000	-0.504	-0.511	-0.132	0.354
T_{iG}	0.241	-0.504	1.000	0.992	-0.622	-0.938
K_{xi}	0.228	-0.511	0.992	1.000	-0.619	-0.947
λ	-0.832	-0.132	-0.622	-0.619	1.000	0.814
T_{ghmax}	-0.492	0.354	-0.938	-0.947	0.814	1.000

	Fit 4 (Subject 3)				
Row/column	V_g	V_i	T_{iG}	T_{ghmax}	λ
V_g	1.000	0.154	0.099	-0.07	-0.791
V_i	0.154	1.000	0.987	-0.774	-0.591
T_{iG}	0.099	0.987	1.000	-0.727	-0.524
T_{ghmax}	-0.07	-0.774	-0.727	1.000	0.662
λ	-0.791	-0.591	-0.524	0.662	1.000

Table B.4: Correlation matrix of the well-determined parameters for Fits 2, 3 and 4 (Subject 3) for the EIC model.

	Fit 5 (Subject 8)					
row/column	V_g	K_{xgI}	T_{iG}	K_{xi}	V_i	T_{ghmax}
V_g	1.00	-0.647	-0.081	-0.335	0.231	0.040
K_{xgI}	-0.647	1.000	-0.652	-0.075	-0.715	0.727
T_{iG}	-0.081	-0.652	1.000	0.381	0.762	-0.925
K_{xi}	-0.335	-0.075	0.381	1.000	-0.226	-0.414
V_i	0.231	-0.715	0.762	-0.266	1.000	-0.723
T_{ghmax}	0.040	0.727	-0.925	-0.414	-0.723	1.000
	Fit 6 (Subject 8)					
row/column	V_g	K_{xgI}	T_{iG}	V_i	λ	T_{ghmax}
V_g	1.000	-0.817	-0.793	-0.805	0.360	0.604
K_{xgI}	-0.817	1.000	0.664	0.703	-0.749	-0.818
T_{iG}	-0.793	0.664	1.000	-0.992	-0.502	-0.730
V_i	-0.805	0.703	0.992	1.000	-0.531	-0.768
λ	0.360	- 0.749	-0.502	-0.531	1.000	0.860
T_{ghmax}	0.604	-0.818	-0.730	-0.768	0.860	1.000

Table B.5: Correlation matrix of the well-determined parameters for Fits 5 and 6 (Subject 8) for the EIC model.

	Fit 8 (Subject 17)					
row/column	V_i	K_{xgI}	T_{iG}	K_{xi}	λ	T_{ghmax}
V_i	1	-0.485	0.879	-0.473	-0.108	-0.607
K_{xgI}	-0.485	1.000	-0.730	-0.349	-0.163	0.771
T_{iG}	0.879	-0.730	1.000	-0.006	-0.045	-0.701
K_{xi}	-0.473	-0.349	-0.006	1.000	0.178	-0.073
λ	-0.108	-0.163	-0.045	0.178	1.000	0.272
T_{ghmax}	-0.607	0.771	-0.701	-0.073	0.272	1.000
	Fit 9 (Subject 17)					
row/column	V_g	K_{xgI}	T_{iG}	V_i	λ	T_{ghmax}
V_g	1.000	-0.402	0.298	0.273	-0.911	-0.881
K_{xgI}	-0.402	1.000	-0.559	-0.591	0.028	0.533
T_{iG}	0.298	-0.559	1.000	0.985	-0.207	-0.626
V_i	0.273	-0.591	0.985	1.000	-0.155	-0.600
λ	-0.911	0.028	-0.207	-0.155	1.000	0.795
T_{ghmax}	-0.881	0.533	-0.626	-0.600	0.795	1.000

Table B.6: Correlation matrix of the well-determined parameters for Fits 8 and 9 (Subject 17) for the EIC model.

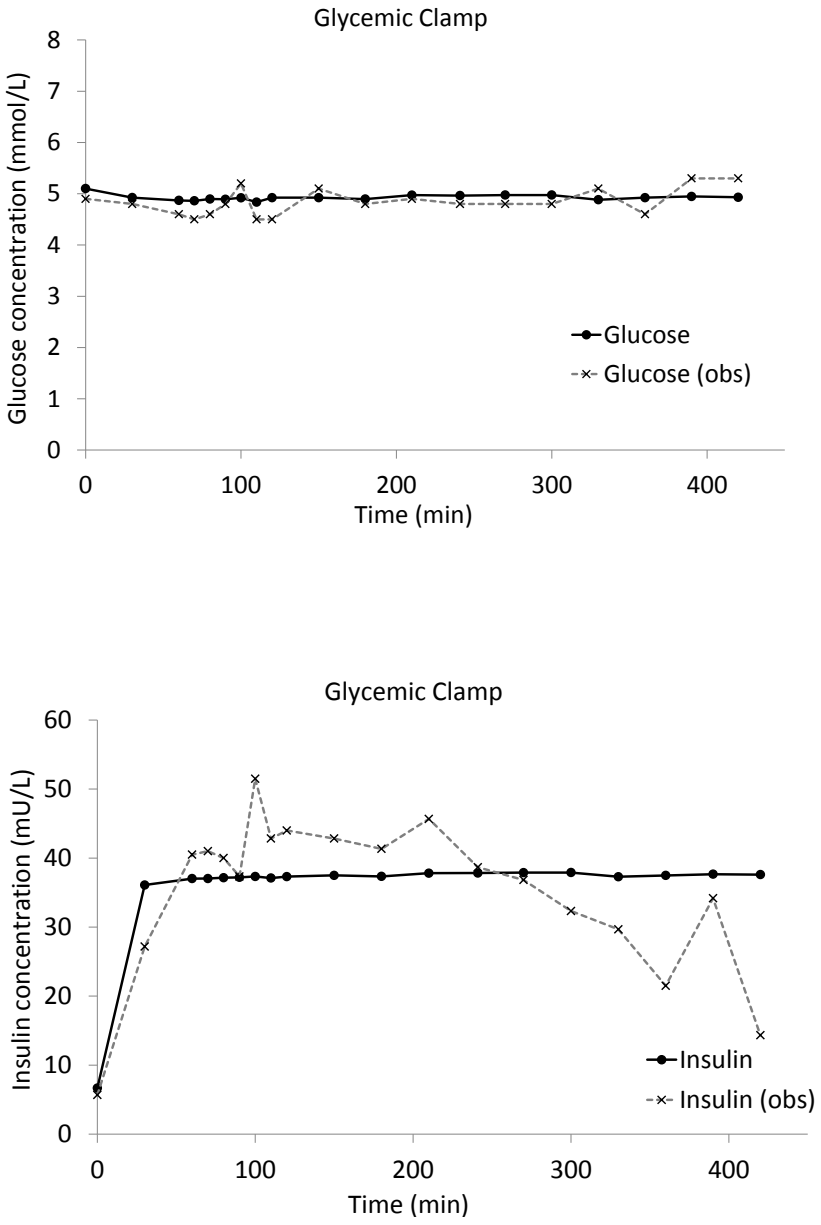

Figure B.1: Glucose and insulin responses for the EIC model, Fit 2 (Subject 3)

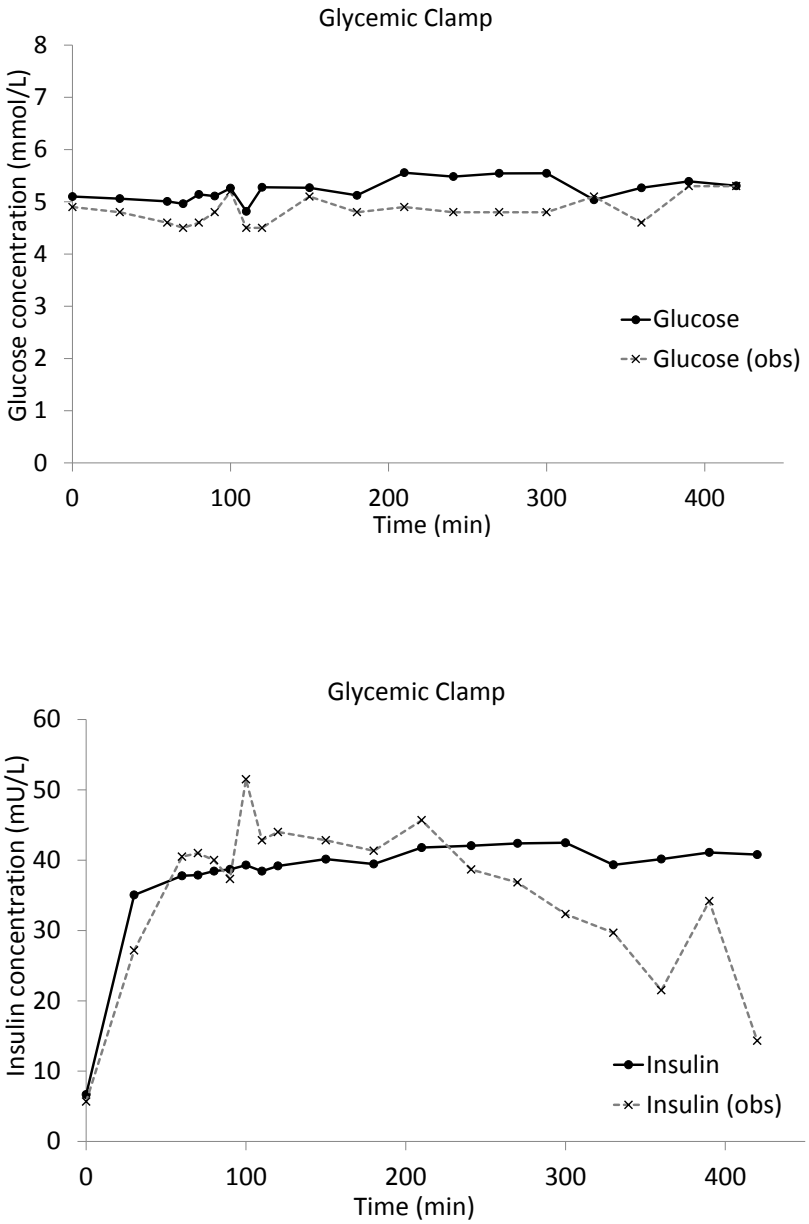

Figure B.2: Glucose and insulin responses for the EIC model, Fit 3 (Subject 3).

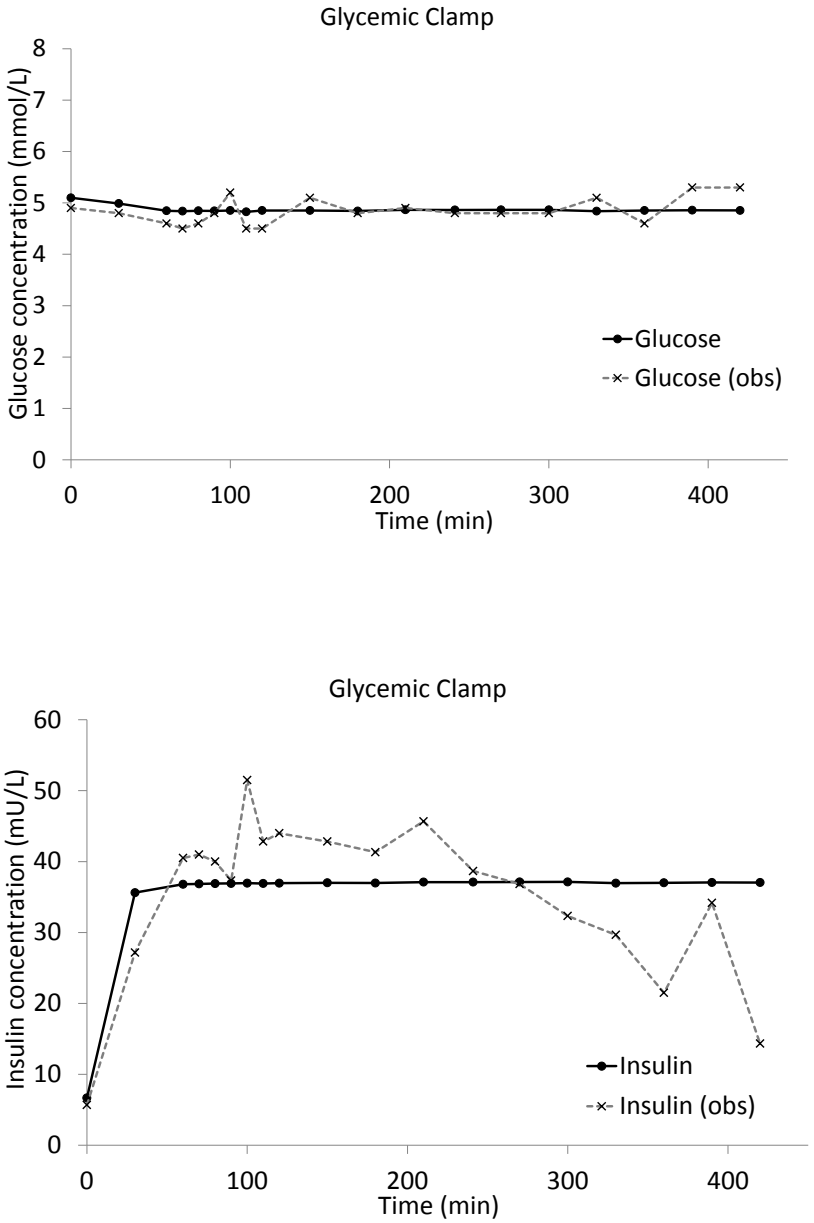

Figure B.3: Glucose and insulin responses for the EIC model, Fit 4 (Subject 3).

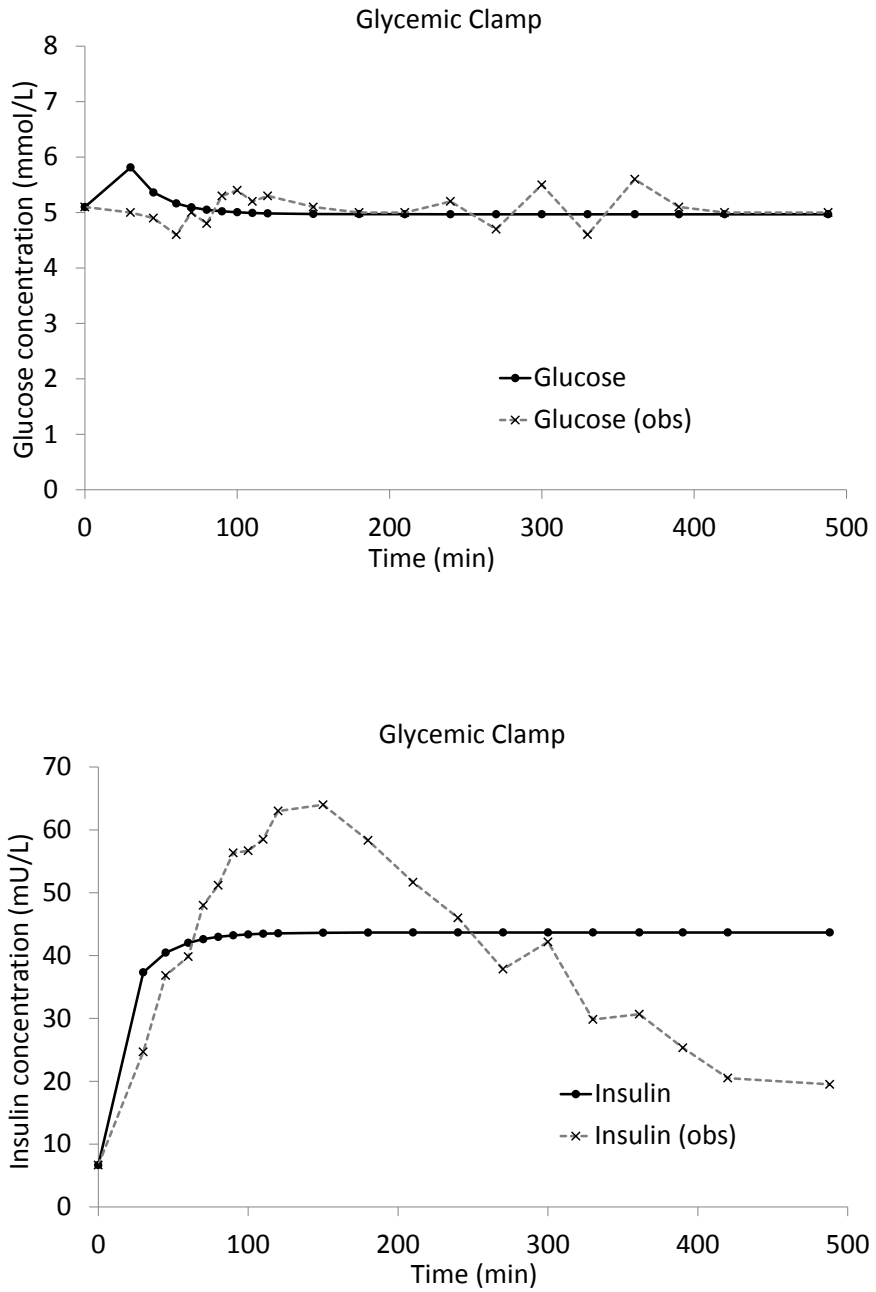

Figure B.4: Glucose and insulin response for the EIC model, Fit 5 (Subject 8)

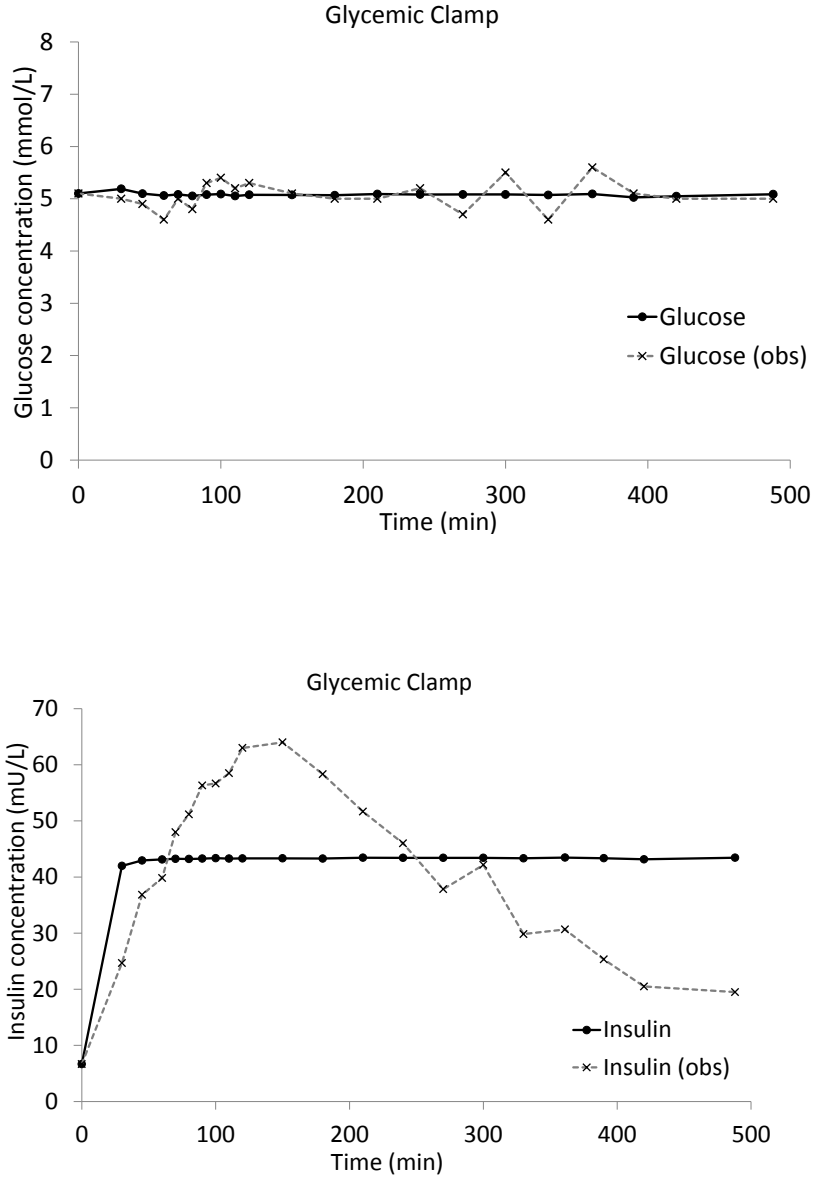

Figure B.5: Glucose and insulin responses for the EIC model, Fit 6 (Subject 8).

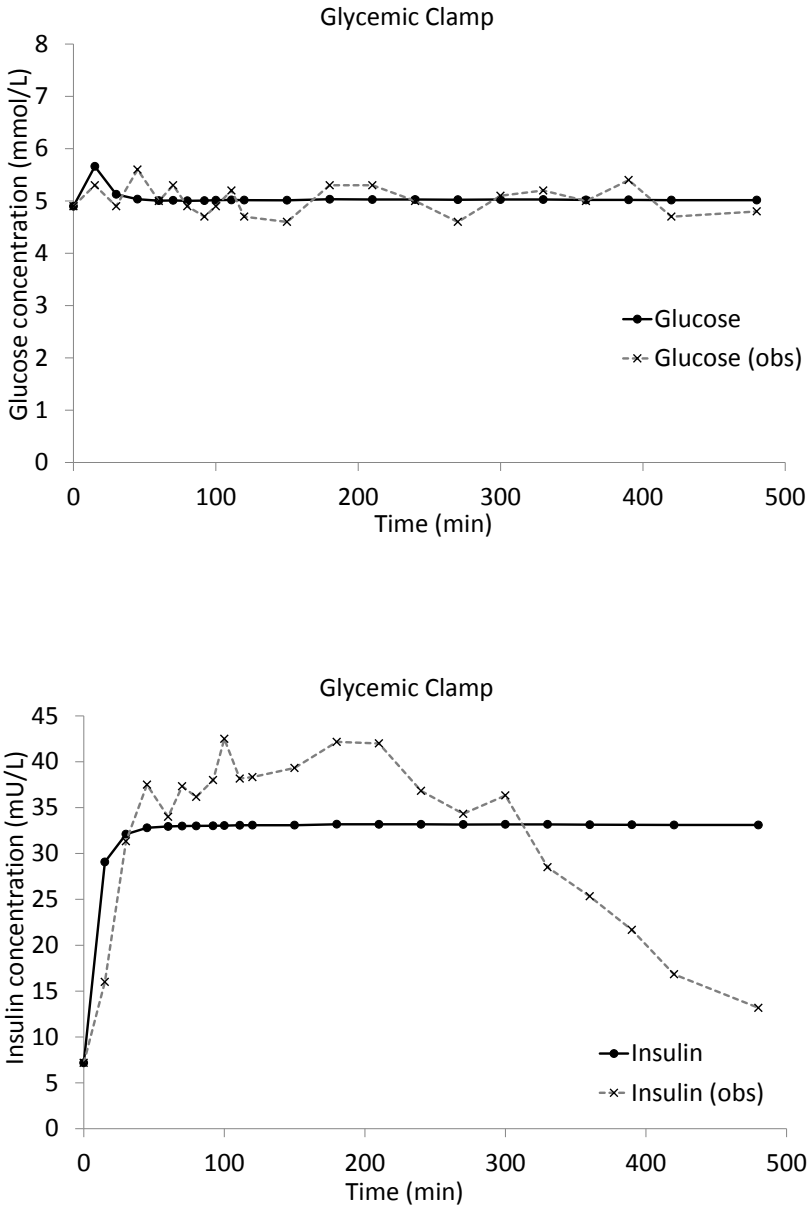

Figure B.6: Glucose and insulin responses for the EIC model, Fit 8 (Subject 17).

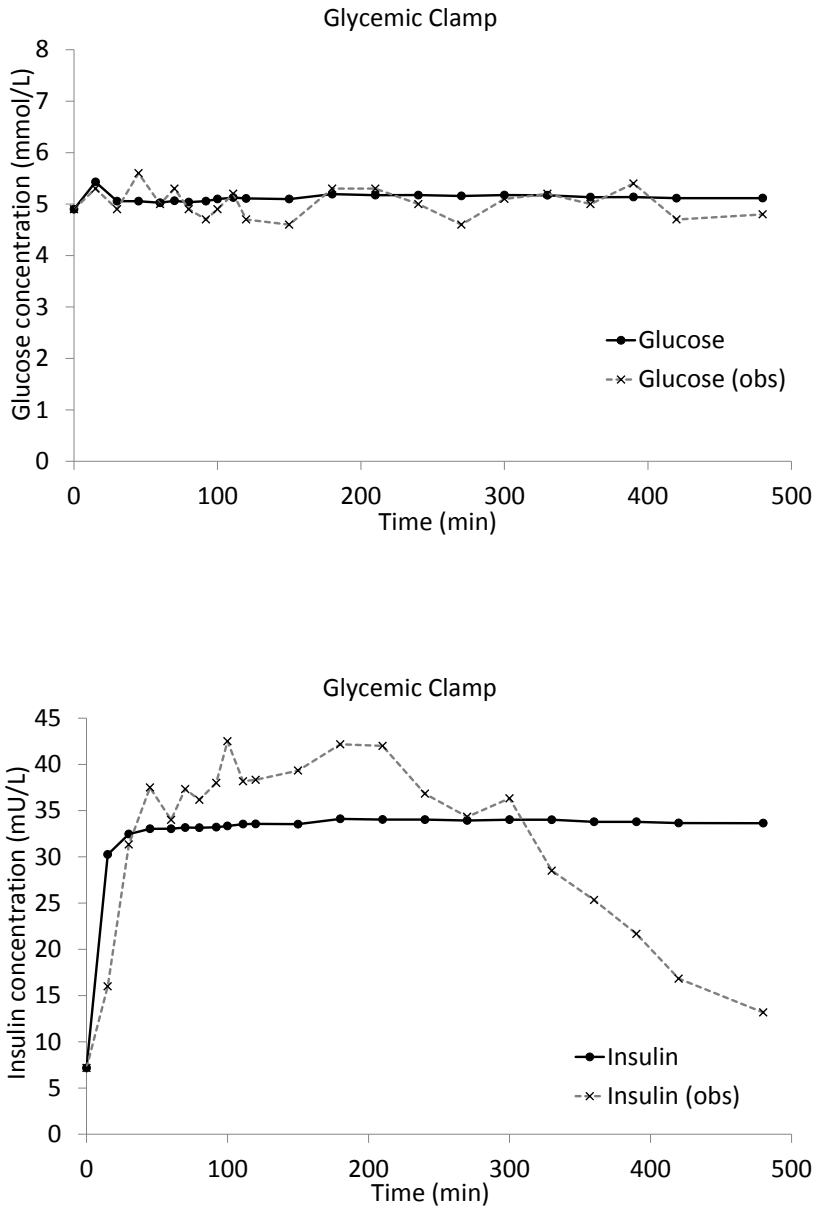

Figure B.7: Glucose and insulin responses fro the EIC model, Fit 9 (Subject 17).

Appendix C

IVGTT data

This Appendix includes the IVGTT data of all subjects, where G (mmol/L) represents the glucose concentration, I (mU/L) represents the insulin concentration and m represents missing data.

Time	Sub. 1		Sub. 2		Sub. 3		Sub. 4		Sub. 5	
(min)	G	I	G	I	G	I	G	I	G	I
0	4.9	6.1	4.5	3.8	5.7	3.7	5.1	9.0	4.5	5.8
1	5.4	6.1	4.9	3.8	5.7	3.7	5.5	9.0	-	-
2	-	-	-	-	-	-	-	-	18.5	5.8
3	9.7	8.3	17.0	15.4	18.3	79.0	19.3	81.9	-	-
5	14.1	78.7	15.6	83.3	17.3	71.2	17.9	127.6	17.2	100.5
6	-	-	-	-	-	-	-	-	15.8	74.4
7	14.1	57.8	14.9	67.4	15.9	50.3	16.1	101.9	-	-
10	-	-	-	-	-	-	-	-	14.2	56.9
11	14.0	37.2	13.4	37.2	14.6	34.0	-	-	-	-
12	-	-	-	-	-	-	14.2	63.8	-	-
15	-	-	-	-	-	-	-	-	12.2	39.3
16	11.9	33.8	11.5	24.2	12.7	25.9	13.4	60.3	-	-
20	-	-	-	-	-	-	-	-	10.5	33.6
21	11.2	26.3	10.3	16.9	11.3	20.4	12.6	47.2	-	-
25	-	-	-	-	-	-	-	-	9.4	24.3
26	10.5	20.6	9.2	13.9	10.0	16.8	11.6	39.1	-	-
30	-	-	-	-	-	-	-	-	8.3	21.2
31	9.9	21.0	8.1	12.8	9.4	14.2	10.6	32.6	-	-
40	-	-	-	-	-	-	-	-	6.9	13.2
41	8.9	18.9	7.0	10.5	7.7	10.9	9.5	32.4	-	-
60	-	-	-	-	-	-	-	-	5.3	6.4
61	7.1	17.6	5.3	6.3	5.8	4.7	7.6	25.3	-	-
80	-	-	-	-	-	-	-	-	4.5	6.1
81	6.1	12.3	4.5	5.4	5.1	3.0	6.2	17.7	-	-
120	-	-	-	-	-	-	-	-	4.2	4.1
121	4.8	5.3	4.2	3.5	-	-	4.8	7.7	-	-
180	-	-	4.6	2.6	-	-	-	-	4.8	2.9
181	4.7	4.3	-	-	5.4	3.0	4.7	6.8	-	-
240	-	-	-	-	-	-	-	-	4.5	3.5
241	4.9	3.9	4.5	3.5	5.7	4.3	5.1	8.3	-	-

Time	Sub. 6		Sub. 7		Sub. 8		Sub. 9		Sub. 10	
(min)	G	I	G	I	G	I	G	I	G	I
0	4.9	3.9	4.8	4.1	4.8	3.2	4.6	24.2	3.8	10.3
1	5.5	3.9	5.4	4.1	-	-	-	-	-	-
2	-	-	-	-	12.1	3.0	-	-	-	-
3	19.8	42.1	15.5	43.7	-	-	9.8	24.2	25.9	10.3
4	-	-	-	-	15.2	49.3	-	-	-	-
5	-	-	15.3	50.5	-	-	10.0	25.9	15.4	28.9
6	15.8	56.4	-	-	14.7	42.1	-	-	-	-
7	14.6	38.9	15.0	44.4	-	-	-	-	14.9	19.4
8	-	-	-	-	-	-	11.6	43.3	-	-
10	-	-	-	-	13.7	26.9	-	-	-	-
11	14.0	22.1	14.5	39.3	-	-	-	-	13.4	15.4
13	-	-	-	-	-	-	6.7	23.9	-	-
15	-	-	-	-	12.6	20.4	-	-	-	-
16	13.1	17.8	13.0	38.4	-	-	-	-	12.8	16.1
18	-	-	-	-	-	-	8.8	21.3	-	-
20	-	-	-	-	11.9	18.4	-	-	-	-
21	11.7	14.4	12.6	33.3	-	-	8.1	18.5	11.8	15.6
25	-	-	-	-	11.3	16.9	-	-	-	-
26	10.8	12.7	11.7	27.7	-	-	7.0	12.6	11.1	15.3
30	-	-	-	-	10.7	14.0	-	-	-	-
31	10.0	11.1	11.5	25.6	-	-	6.3	9.1	10.6	14.2
40	-	-	-	-	9.2	14.5	-	-	-	-
41	8.7	9.2	10.4	23.5	-	-	5.6	7.6	9.6	16.0
60	-	-	-	-	7.4	11.2	-	-	-	-
61	6.8	7.0	8.4	17.8	-	-	4.5	3.9	8.0	20.7
80	-	-	-	-	5.9	6.6	-	-	-	-
81	5.4	5.3	7.2	14.4	-	-	-	-	6.3	13.5
120	-	-	-	-	4.5	3.2	-	-	-	-
121	4.5	3.5	5.4	7.0	-	-	4.4	2.6	4.7	5.8
181	-	-	4.6	3.6	-	-	-	-	4.2	4.8
241	-	-	4.8	5.0	-	-	-	-	3.8	3.4

Time	Sub. 11		Sub. 12		Sub. 13		Sub. 14		Sub. 15	
(min)	G	I	G	I	G	I	G	I	G	I
0	4.6	39.6	4.9	45.4	4.5	m	4.7	5.2	5.0	4.3
1	-	-	-	-	5.0	m	-	-	5.0	4.3
2	-	-	-	-	-	-	5.8	5.3	-	-
3	14.8	39.6	16.7	45.4	13.3	10.2	-	-	15.5	29.0
4	-	-	-	-	-	-	13.3	94.2	-	-
5	13.9	49.6	16.2	51.0	15.2	62.5	-	-	14.5	113.5
6	-	-	-	-	-	-	13.1	86.7	-	-
7	13.3	44.2	14.8	43.2	14.7	48.1	-	-	14.6	82.3
10	-	-	-	-	-	-	12.7	58.1	-	-
11	12.5	24.4	13.6	29.1	11.8	26.3	-	-	13.1	46.7
15	-	-	-	-	-	-	10.6	35.1	-	-
16	11.7	17.8	13.1	21.7	8.6	16.7	-	-	10.8	31.7
20	-	-	-	-	-	-	10.1	30.5	-	-
21	11.2	17.4	11.9	17.3	-	-	-	-	10.1	21.6
24	-	-	-	-	5.4	8.4	-	-	-	-
25	-	-	-	-	-	-	9.1	21.9	-	-
26	10.9	15.8	10.4	14.1	6.5	6.9	-	-	8.3	15.7
30	-	-	-	-	-	-	7.4	18.1	-	-
31	10.2	14.5	10.0	12.5	4.9	6.3	-	-	8.1	13.4
40	-	-	-	-	-	-	6.5	13.1	-	-
41	9.4	15.1	8.7	12.2	3.0	3.6	-	-	6.3	8.5
60	-	-	-	-	-	-	4.8	6.5	-	-
61	7.7	15.3	7.1	9.1	-	-	-	-	5.7	3.0
80	-	-	-	-	-	-	4.8	6.5	-	-
81	6.7	10.6	6.0	7.1	4.9	3.1	-	-	5.2	3.5
120	-	-	-	-	-	-	4.8	3.5	-	-
121	4.8	4.8	-	-	4.8	2.6	-	-	-	-
126	-	-	-	-	-	-	-	-	5.1	2.9
180	-	-	-	-	-	-	4.9	3.0	-	-
181	3.7	5.0	6.0	3.0	-	-	-	-	5.2	2.5
241	-	-	-	-	-	-	-	-	5.0	2.6
246	-	-	-	-	-	-	4.7	2.7	-	-
m represents data missing										

Time	Sub. 16		Sub. 17		Sub. 18		Sub. 19		Sub. 20	
(min)	G	I	G	I	G	I	G	I	G	I
0	4.8	m	4.8	23.1	4.7	m	4.7	m	4.9	3.3
1	5.4	m	-	-	5.6	m	4.7	m	-	-
2	-	-	-	-	-	-	-	-	10.3	3.3
3	22.0	m	12.6	23.1	10.2	19.0	15.5	23.1	-	-
4	-	-	-	-	-	-	-	-	13.1	14.2
5	17.1	36.0	14.8	42.1	12.1	33.1	13.3	41.3	-	-
6	-	-	-	-	-	-	-	-	13.0	10.6
7	16.2	26.2	14.4	31.8	-	-	12.6	31.9	-	-
8	-	-	-	-	13.0	30.1	-	-	-	-
10	-	-	-	-	-	-	-	-	12.5	6.7
11	13.7	15.4	14.1	18.6	12.9	22.0	12.7	18.7	-	-
15	-	-	-	-	-	-	-	-	12.5	6.7
16	12.9	12.6	12.8	14.5	12.0	19.5	11.2	15.6	-	-
20	-	-	-	-	-	-	-	-	9.8	5.6
21	11.4	12.7	11.8	13.2	11.3	19.0	9.9	11.8	-	-
25	-	-	-	-	-	-	-	-	9.5	5.7
26	10.2	10.4	10.7	13.0	10.7	17.8	9.0	8.4	-	-
30	-	-	-	-	-	-	-	-	8.8	4.8
31	9.1	9.3	10.0	12.6	10.4	18.4	7.7	6.1	-	-
40	-	-	-	-	-	-	-	-	7.5	6.4
41	7.6	9.2	8.8	12.4	9.4	19.3	6.7	4.1	-	-
60	-	-	-	-	-	-	-	-	5.8	3.8
61	-	-	6.6	7.2	7.7	19.6	5.2	3.1	-	-
81	-	-	6.6	4.6	6.5	9.6	-	-	-	-
181	-	-	-	-	-	-	4.5	2.8	-	-
241	-	-	-	-	-	-	4.7	3.5	-	-

m represents data missing

Time	Sub. 21		Sub. 22		Sub. 23		Sub. 24		Sub. 25	
(min)	G	I	G	I	G	I	G	I	G	I
0	4.8	5.8	4.8	3.8	4.7	m	4.8	10.4	5.0	m
2	20.8	5.3	19.1	5.8	12.5	22.7	-		7.0	,
3	-	-	-	-	-	-	10.1	10.4	-	-
4	15.2	55.7	14.4	26.1	13.0	22.3	-	-	15.7	41.8
5	-	-	-	-	-	-	12.9	34.5	-	-
6	15.1	40.8	14.2	23.7	12.2	16.9	-	-	14.7	34.3
7	-	-	-	-	-	-	13.4	38.4	-	-
10	14.0	36.6	14.6	22.0	12.5	13.4	-	-	13.0	22.1
11	-	-	-	-	-	-	13.6	37.8	-	-
15	12.7	29.1	12.2	18.6	12.5	16.8	-	-	10.5	14.7
16	-	-	-	-	-	-	13.0	35.6	-	-
20	11.5	24.3	11.4	20.3	11.2	12.4	-	-	9.0	12.1
21	-	-	-	-	-	-	11.9	32.1	-	-
25	11.0	24.5	10.4	20.3	10.4	15.2	-	-	7.6	9.3
26	-	-	-	-	-	-	11.1	32.9	-	-
30	9.8	23.3	9.9	17.1	9.5	12.8	-	-	4.6	9.9
31	-	-	-	-	-	-	10.7	30.4	-	-
40	8.3	25.6	8.4	15.3	8.1	15.9	-	-	6.0	7.6
41	-	-	-	-	-	-	9.2	28.3	-	-
60	6.2	15.8	6.7	16.3	6.1	7.5	-	-	6.7	3.2
61	-	-	-	-	-	-	7.5	25.0	-	-
80	4.7	11.5	5.7	6.6	5.0	4.6	-	-	4.6	2.8
81	-	-	-	-	-	-	6.3	22.9	-	-
120	4.8	8.3	4.8	3.3	-	-	-	-	-	-
121	-	-	-	-	-	-	4.5	8.7	-	-
180	-	-	4.7	3.6	4.7	2.6	-	-	-	-
181	5.1	4.4	-	-	-	-	4.5	8.1	-	-
239	4.8	5.8	-	-	-	-	-	-	-	-
240	-	-	4.8	3.8	-	-	-	-	-	-
241	-	-	-	-	-	-	4.5	6.7	-	-

m represents data missing

Time	Sub. 26		Sub. 27		Sub. 28	
(min)	G	I	G	I	G	I
0	5.0	16.8	4.6	10.0	4.6	m
2	-	-	-	-	13.9	13.3
3	15.9	16.8	7.9	10.0	-	-
4	-	-	-	-	14.9	33.3
5	16.2	38.2	10.0	20.9	-	-
6	-	-	-	-	14.3	38.5
7	16.0	33.8	10.4	26.9	-	-
10	-	-	-	-	14.4	24.6
11	14.6	23.8	10.7	18.5	-	-
15	-	-	-	-	12.6	21.0
16	12.6	19.0	10.0	14.0	-	-
20	-	-	-	-	11.6	18.1
21	12.1	15.8	9.6	12.9	-	-
25	-	-	-	-	10.1	15.8
26	10.9	14.6	9.0	13.1	-	-
30	-	-	-	-	9.3	15.6
31	10.7	11.1	8.9	13.3	-	-
40	-	-	-	-	7.8	15.2
41	9.4	9.5	8.3	14.4	-	-
50	-	-	-	-	6.4	11.0
61	7.7	7.2	-	-	-	-
62	-	-	7.3	12.1	-	-
70	-	-	-	-	4.1	5.4
81	6.0	3.9	4.7	7.6	-	-
110	-	-	-	-	3.9	2.9
121	4.7	2.9	6.2	5.3	-	-
181	-	-	4.4	4.0	-	-
241	-	-	4.6	4.6	-	-

m represents data missing