Mathematical Modelling of Blood Glucose Regulation

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Abstract

Exercise is beneficial for all individuals; it lowers blood pressure, keeps the heart healthy and increases insulin sensitivity. Recent studies have shown the power that regular exercise has to improve metabolic health, which in turn works to prevent and to reverse the onset of the widespread epidemics of type 2 diabetes (T2DM). However, diabetics taking insulin are required to meticulously plan exercise around meals and intake of insulin as they face an increased risk of hypoglycaemia from physical activity, which can discourage them from taking part.

This thesis describes the use of systems of ordinary differential equations to model the effects of exercise on the glucose regulatory system, for both healthy and diabetic individuals. A particular focus is given to the role of glucagon, whose role is often neglected in glucoregulatory models, and its ability to enhance hepatic glucose production and so to prevent hypoglycaemia. Models of glucose-insulin-glucagon dynamics are first developed to describe an Intravenous glucose tolerance test (IVGTT), as the processes involved are simpler than in exercise and already widely modelled for glucose and insulin, thus is a good basis for validating the incorporation of glucagon.

Mathematical models are used as tools within biological applications as they allow for an investigation into the dynamics that are involved in complex regulatory processes. The mathematical models in this thesis serve as accurate tools to predict blood glucose levels during exercise for both a non-diabetic and type 1 diabetic individual (T1DM) and emphasise exercise as a key element in the prevention of T2DM. By mathematically modelling the system and the mechanisms that occur to maintain glucose homeostasis an insight is gained into what the principal factors are for the greatest increase in insulin sensitivity and for the reduction in the likelihood of either hypoglycaemic or hyperglycaemic episodes. This may lead to recommendations for exercise plans which not only provide the greatest benefits for everyday health ant to assist with preventing the onset of diabetes but also to offer safer regimes for individuals with T1DM.

Acknowledgements

Undertaking an MSc has been a challenging yet enjoyable experience for which I would like to thank Oxford Brookes University for the opportunity.

I would like to thank my supervisor, Dr. Stewart Chidlow, for his confidence in me over the past year and for making this opportunity available to me. It has been an absolute pleasure to have been able to work and discuss ideas with someone who shares my enthusiasm in my work. It was the continuous support and encouragement that kept me focused, steered me in the right direction and has allowed for me to succeed in mathematics. I am very grateful for his participation and input which has helped me realise and take the right steps towards a career in which I am passionate for.

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I am grateful to my parents for their endless support and ability to find a positive twist to any issue that arose throughout the project.

Finally I would like to thank the Wheatley coffee crew for our frequent breaks in Starbucks which undoubtedly fuelled creativity.

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Definitions

Asymptotic Stability - A point *x is* an asymptotically stable equilibrium *point* of f if:

1. It is a Lyapunov stable equilibrium point of f.
2. There exists some open neighbourhood *O of x such that,* for any $x_i \in$

, x(t) converges to x as t approaches infinity. (LaValle, 2006)

Basal level - A basal level refers to a standard or reference state and that is considered as a convenient standard measurement.

Buckingham π Theorem - Consider a system with variables $x_1, \ldots\ldots, x_k$ and parameters $p_1, \ldots\ldots, p_l$, in which *m* fundamental dimensions are involved. Then *k+l-m* dimensionless quantities q_i can be defined, which are products and quotients of the original variables and parameters. Each (scalar) model equation

$$(x_1, \ldots\ldots, x_k, p_1, \ldots\ldots, p_l) = 0, \quad (1)$$

Between the $x_i$and p_i of a mathematical model can be replaced with a corresponding relation between the q_i.

$$f * (q_1, \ldots., q_{k+l-m}) = 0, \quad (2)$$

Therefore, it can be determined that the system can be described with 16 dimensionless quantities.

$$f(\mathrm{G}, \mathrm{X}, \mathrm{I}, \mathrm{E}, p_1, p_2, p_3, p_4, p_5, p_6, p_7, p_8, p_9, G_b, I_b, E_b, G_0, I_0\ ), \quad (3)$$

Between the variables and parameters of a mathematical model can be replaced with the corresponding relation between the dimensionless quantities q_i:

$$f^*(q_1, \ldots\ldots, q_{16}) = 0, \quad (4)$$

(Van Groesen and Molenaar, 2007)

Catecholamines - Stimulate the release of glucagon, and sometimes release of them are induced by glucagon. Released from adrenal medulla. They are a class of aromatic amines including neurotransmitters such as adrenaline and dopamine.

Critical Point In a system of autonomous differential equations the critical points refer to a set of points where all equations are equal to 0, i.e. $\frac{dG}{dt} = \frac{dI}{dt} = \frac{dE}{dt} = 0$. In other words, they are the points where the function has a horizontal tangents and are considered as the roots of the system. Critical points are considered to determine the long term behaviour of a system.

Endogenous – Originating within the body

Exercise Intensity – Amount of expended energy during exercise. It determines sources of fuel used and other adaptations to be made by the body.

Exogenous – Originating outside of the body

Glucagon – The counter regulatory hormone for glucose. Glucagon is released when glucose levels are too low.

Glucagon Sensitivity (S_E) - Ability to produce glucagon when blood glucose are low, in order to raise glucose levels back into the desired range.

Glucose Effectiveness (S_G) – The ability to dispose of excess glucose during hyperglycaemic periods

Gluconeogenesis - The formation of glucose in the liver and kidneys from compounds such as lactate, pyruvate, amino acids and glycerol.

Glucose tolerance - The body's ability to dispose of carbohydrate, effected by pancreatic responsiveness and insulin sensitivity. (Bergman et al, 1989)

Glycaemia - The presence of glucose in the blood.

Hepatic – Relating to the liver

Hexameric – Referring to a molecule comprising of six subunits.

Hyperglycaemia - Hyperglycaemia refers to an excess concentration of glucose in the plasma and is typically defined at a fasting blood glucose level of $\geq 126 mg/dl$ $(7 mmol/L)$ (Geuillermo et al,. 2009).

Hypoglycaemia - Hypoglycaemia refers to a lack of glucose in the plasma and is typically defined as a blood glucose level of $\leq 60 mg/dl$ $(3.3 mmol/L)$ (Miller et al., 2001).

Insulin Sensitivity (S_I) - Insulin sensitivity describes how sensitive the body is to the effects of insulin. The higher the sensitivity, the less insulin required to lower blood glucose (Insulin Sensitivity, 2016).

Interstitial space - Fluid filled areas surrounding space of a tissue.

Intravenously – Entering through a vein

Locally Lipschitz-continuous - The function f is locally Lipschitz-continuous, if for each $z \in R^n$there exists an L>0 such that **f** is Lipschitz-continuous on the open ball of centre z and radius L

$$B_L(z) \coloneqq \{y \in R^m : ||y - z|| < L\}.$$

(Van Hassel, 2006)

Lyapunov stable - Let $x' = (x)$, $(x^*) = 0$ where x^* is in the interior of $\Omega \subset R^n$. Assume that $V: \Omega \to R$ is a ^{1} function. If:

1. $(x^*) = 0$
2. $(x) > 0$, for all $x \in \Omega$, $x, = x^*$

1. $V'(x) \leq 0$ along all trajectories of the system in $\Omega \to x^*$ is locally stable. Furthermore, if also

2. $V'(x) < 0$ for all $x \in \Omega$, $x \neq x^* \to x^*$ is locally asymptotically stable.

(Lyapunov Stability, 2015)

Negative Feedback System – Output of a system is fed back to reduce or increase the output.

Non-dimensionalization - Non-dimensionalization refers to the process of transforming a series of equations to dimensionless (unitless) forms by rescaling the model variables. (Computational Ecology & Epidemiology Study Group, 2012)

Routh-Hurwitz Criteria – Given an nth order linear constant coefficient equation of the form:

$$p(D)z = z^n + a_1 z^{n-1} + a_2 z^{n-2} + \cdots + a_n z = 0 \tag{5}$$

with real coefficients $\{a_n\}_j^n = 1$.

$$D_1 = \alpha_1, D_2 = \det\begin{bmatrix} a_1 & a_3 \\ 1 & a_2 \end{bmatrix}, \ldots\ldots, D_k = \det\begin{bmatrix} a_1 & a_3 & a_5 & \cdots & a_{2k-1} \\ 1 & a_2 & a_4 & \ldots & a_{2k-2} \\ 0 & a_1 & a_3 & \ldots & a_{2k-3} \\ 0 & 1 & a_2 & \ldots & a_{2k-4} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & a_k \end{bmatrix} \tag{6}$$

where $a_j = 0$ if $j > n$.

Then the roots of $P(\lambda)$, the characteristic polynomial of (6) have negative real parts if and only id $D_k > 0$ for all $k = 1, \ldots, n$.

Stability - Consider a differential equation $x'(t) = f(t, x(t))$ where $x(t) \in R^n$. We assume that f is continuous and locally Lipschitz (see definition) with respect to the second variable.

Let $t \to (t, t_0, x_0)$ denote the maximally defined solution of the equation satisfying the initial condition $(t_0) = x_0$.

Let $: [t_0, \infty) \to R^n$ be a solution of the differential equation.

1. The solution ϕ is stable on $[t_0, \infty)$ if, for every $\varepsilon > 0$, there is a $\delta > 0$ such that whenever $|\phi(t_0) - x_0| < \delta$, the solution $x(t, t_0, x_0)$ is defined for all $t \in [t_0, \infty)$ and$|(t) - x(t, t_0, x_0)| < \varepsilon, \forall\, t \geq t_0$.

2. ϕ is asymptotically stable (see definitions and abbreviations) (on $[t_0, \infty)$) if it is stable and, given ε as above, there is a $\delta_1 < \delta$ such that whenever $|\phi(t_0) - x_0| < \delta_1$ $\lim_{t\to\infty} \phi(t) - x(t, t_0, x_0)| = 0$. If ϕ is not stable, it is said that the solution is unstable. This means that there is some $\varepsilon > 0$ such that for every $\delta > 0$ there is some point x_0 with $|\phi(t_0) - x_0| < \delta$ such that $|\phi(t_1) - x(t_1, t_0, x_0)| \geq \varepsilon$ for some time $t_1 \in [t_0, \infty)$. (Schovanac and Gilliam, 1999)

Abbreviations

IVGTT – Intravenous glucose tolerance test

OGTT – Oral glucose tolerance test

T1DM – Type 1 Diabetes Mellitus

T2DM – Type 2 Diabetes Mellitus

VO_2max = measure of the maximum volume of oxygen that an athlete can use. It is measured in millilitres per kilogramme of body weight per minute (ml/kg/min) / VO_2max is defined as the highest attainable rate of aerobic metabolism during the performance of dynamic work that exhausts the subject within 5–10 min and it is internationally accepted as an index of one's cardiorespiratory fitness (Bandyopadhyay, 2014)

PVO_2max – Percentage of VO_2max

Chapter 1 Introduction

1.1. Motivation for Study

In 2014, it was reported that, in England alone, 3.2 million people (7.4% of the population) had either been diagnosed with or were unaware that they had diabetes (Gatineau et al., 2014). This number is predicted to escalate to 5 million by 2025 (Diabetes.co.uk, 2016) primarily due to changes in lifestyle related to economic development (Amos et al., 1997).

Complications frequently associated with diabetes include retinopathy, nephropathy, peripheral neuropathy and blindness (Derouich and Boutayeb, 2002), projecting the disease to be the 7th leading cause of global deaths by 2030 (World Health Organisation, 2016).

Evidently, diabetes is a growing problem, and a great amount of research goes into understanding the development of the disease in addition to how we can prevent and treat diabetes. The use of mathematical models as an approach to aid our understanding of glucose regulation has grown rapidly over recent years, providing new insights into the underlying mechanisms involved and the dynamic behaviour of the complex biological system (Ajmera et al., 2013). Practical uses of these models include the assessment of insulin sensitivity and glucose effectiveness (Vicini et al. 1997), as tools for automated insulin dosage adjustment based on glucose measurements (Lehmann and Deutsch, 1992) and as valuable elements for the progression of the development of an artificial pancreas (Herrero et al. 2013).

Despite the vast number of mathematical models developed there is still a requirement for further modelling of the glucose regulatory system, in order to bridge the gap between the growing amounts of knowledge and data gained from experimental approaches (Ajmera et al. 2013). A lack of reliable, predictive and suitable models is also considered a hindrance to the development of diabetes treatments and artificial pancreases (Huang et al., 2012), (Herrero et al. 2014).

1.2. The Glucose Regulatory System

Used and stored for energy, glucose is an important source of fuel and in order to maintain good health it is essential that plasma glucose levels are maintained within the homeostatic range, which typically lies between 70-110mg/dl (Makroglou et al., 2006) or 3.8-6.1mmol/L in SI units. This thesis will use the conventional units for glucose, insulin and glucagon (mg/dl, μU/ml and pg/ml) for comparison purposes, as they are used in the majority of mathematical models. This will also simplify the analysis of parameter values obtained in the proposed models to the acceptable ranges available in existing literature. The regulation of blood glucose levels ensures that a sufficient amount of glucose is delivered to cells, where it is then broken down and used as an energy source to fuel cellular processes such as the functioning of the brain and the physical movement of muscles. This process of glucose regulation, the components involved and relationships they have with each other are referred to as the glucose regulatory system.

Glucose appears in the system as a result of either internal production by the liver or from an external administration, such as a meal containing carbohydrates, which typically takes 15-30 minutes after consumption to increase blood sugar levels. Glucose is removed from the system by conversion into glycogen, used as a form of energy by the brain, red blood cells and the peripherals, and, when there is an excessive amount of glucose, it is cleared by the kidneys or stored as fat.

Glucose homeostasis is primarily regulated by two hormones, insulin and glucagon, which are released in response to signals as they travel through the circulatory system. They regulate the system by ensuring the plasma glucose concentration stays in the desired range, thus not getting too high (hyperglycaemic state) or too low (hypoglycaemic state). Both hormones target the muscles, adipose tissues and liver (MacLaren and Morton, 2012), affecting various biochemical processes as a means of regulation. It is the ratio of glucagon to insulin that primarily controls fuel mobilization (Plowman and Smith, 2010).

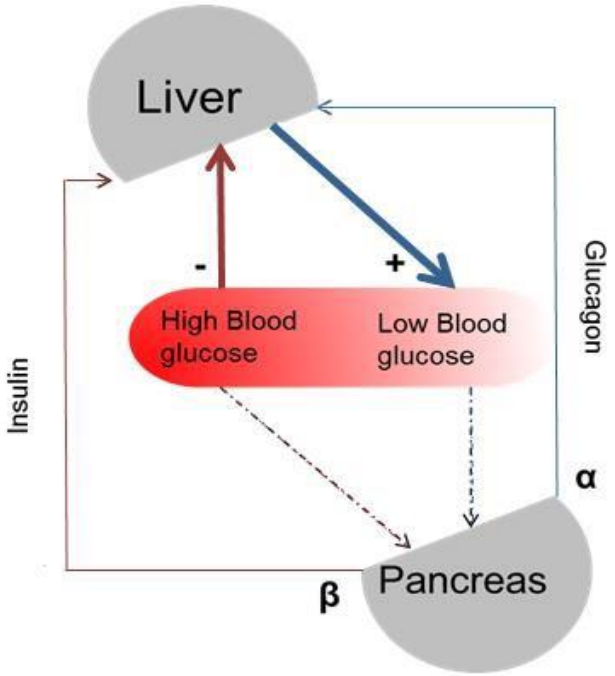


Figure 1.1: The blood glucose-insulin-glucagon feedback system

Insulin is released continuously by the beta cells in the pancreas into the blood stream, which, for healthy patients, means a basal insulin level of <25 μU/mL (Buppajarntham, 2014), and is cleared from plasma by the liver. An increase in insulin secretions occurs in response to a high concentration of blood glucose; for example: after consuming a meal, insulin is released to lower glucose levels, restoring the homeostatic state by stimulating anabolic reactions for the macronutrients consumed. The plasma glucose threshold for insulin secretion is given typically as 81mg/dl (Goodwin, 2010) so that when glucose falls to this threshold value insulin secretion is suppressed. However this value will differ between individuals.

Glucagon is produced by the alpha cells in the pancreas and is recognised as the primary counter regulatory hormone to counteract a fall in glucose levels. Typically the threshold value of glucose levels for glucagon release is defined as any concentration less than 67-80mg/dl (Goodwin, 2010) (Liu and Tang, 2008) . The role of Glucagon is to mobilize fuel (Plowman and Smith, 2010) and is realised during periods of starvation or prolonged physical activity, where the level of circulating plasma glucose is not sufficient to meet the individual's demands for energy. Glucagon achieves an increase in plasma glucose through the means of promoting both glycogenolysis and gluconeogenesis (Teixeira and Malin, 2008).

Glucose is cleared from the plasma by a number of ways; hepatic uptake, in which glucose is stored by the liver (Moore et al., 2012), utilization by the brain and red blood cells, clearance by the kidneys when glucose levels are excessive and uptake by the peripherals (Sulston et al., 2006). Glucose uptake by the peripherals (muscle and tissue) is considered as insulin-dependent glucose uptake, as insulin activity is required to absorb glucose. The liver is also considered as insulin-dependent, despite its ability to respond independently to high glucose levels, as the majority of the liver's functions for glucose regulation require insulin (Brandt, 1999).

1.3. Diabetes

Insufficient secretion or a hypoactivity of insulin can result in diabetes mellitus, a metabolic disorder characterised by persistent hyperglycaemia. Diabetes is typically categorised as either type 1 or type 2.

Type 1 diabetes, typically diagnosed earlier in life, is an autoimmune disease leading to the destruction of the pancreatic beta-cells (Magdelaine et al, 2015), whereby the functionality of the pancreases is severely impaired or it is unable to naturally secrete insulin in response to high glucose levels. In order to prevent fatality, the patient depends on regular exogenous doses of insulin to maintain homeostatic levels of blood glucose.

Type 2 diabetes (T2DM) is most commonly diagnosed in the older generation, with the majority of adults diagnosed with the disease in 2012 aged between 45 and 64 (Krucik, 2014). The most significant factors linked to the cause of T2DM are being overweight, abdominal obesity and physical inactivity (Stumvoll et al. 2005). The aetiology of T2DM includes β-cell dysfunction and, for the majority of diabetic individuals, insulin resistance (Bergman et al. 2002), i.e. resistance to insulin-stimulate glucose uptake (Reaven, 1988).

1.4. Glucose Tolerance Testing

Diabetes is provisionally diagnosed and classified by a fasting glucose of ≥126mg/dl (American Diabetes Association, 2004). Often if an individual is thought to be at risk of developing or having diabetes they will undergo a glucose tolerance test (GTT), which tests their ability to breakdown glucose. The patient must arrive for the test in a fasting state, due to the fact that an impaired β-cell function manifests itself in a different manner in fasting and glucose-stimulated conditions (Del Prato et al. 2002). There are two different types of GTTs: the oral glucose tolerance test (OGTT) and the intravenous glucose tolerance test (IVGTT).

During an OGTT a patient will receive an oral solution containing 75g of glucose at the beginning of the test. Blood glucose samples are then taken every 15 minutes for the first hour, and every 30 minutes for the following two hours. The diagnosis of diabetes is based on the ability of the system to clear the glucose from the plasma within a reasonable time frame, which is typically between 90-120 minutes in a healthy individual.

The IVGTT follows a similar protocol as the OGTT the main difference being that the IVGTT consists of a bolus of glucose being administered intravenously.

1.5. Thesis Outline

This thesis is structured as follows:

Chapter 1 – Introduction and Background

The first chapter will provide an introduction to the basic anatomy of the glucose regulation system, defining diabetes is along with the impacts it has on the system, and the problems involved with blood glucose regulation which motivate this study.

Chapter 2 – Introduction to Glucose Regulation Models

A description of the key models developed for glucose regulation will be presented and critically reviewed.

Chapter 3 – Development of Mathematical Models with Glucagon Dynamics

Chapter 3 will contain the implementation of the primary hormone Glucagon into a glucose regulatory model, since it is the key regulatory hormone in periods of low glucose concentrations. This will lead to the development of a model accounting for the physiological effects on the system during exercise. This chapter includes the implementation of the proposed models into MATLAB, and a discussion of the simulated results.

Chapter 4 – Introduction to Exercise

In this chapter a summary of the key exercise induced effects on the glucose regulatory system is given in addition to the motivation for developing a model for exercise.

Chapter 5 – Glucagon Models for Exercise

Chapter 5 presents two mathematical models designed to be capable of predicting blood glucose levels during exercise. The models are implemented in MATLAB followed by a discussion of the model proposed.

Chapter 6 – Glucagon Minimal Model for Exercise with Exogenous Insulin Administration

Chapter 6 extends the models proposed previously in the thesis to consider exogenous insulin supply.

Chapter 7 – Conclusion and Future Work

This chapter concludes the work of the thesis, discussing the accuracy of the models proposed and further work for the study.

Chapter 2 Introduction to Glucose-Regulation

2.1. Introduction to Modelling Glucose-Insulin Dynamics

The use of mathematical models within biological applications has become increasingly frequent due to their ability to act as powerful tools in improving our understanding of complex biological systems. Mathematical models allow researchers to investigate how complex regulatory processes are connected and how disruptions of these processes may contribute to the development of disease (Fischer, 2008). Therefore, it is no surprise that mathematical models frequently appear in research addressing the issue of the growing prevalence of diabetes.

During the past five decades, there has been an increase in the number of mathematical models available in literature, created to improve our understanding of the complex behaviour and relationships involved in glucose homeostasis.

Mathematical models for blood glucose dynamics can allow for measurements of important aspects within the glucose regulatory system, such as the beta cell responsivity, insulin sensitivity and glucose effectiveness. Assigning numerical values to these aspects admits an insight into the metabolic portrait of an individual, and can be perceived as whether the individual is healthy, facing the onset of or has developed diabetes. As well as diagnostic purposes, mathematical models are also used as epidemiological tools within diabetes management, assessing means of controlling the disease and analysing other factors affecting the regulatory system. In more recent developments, predictions of blood glucose levels made by mathematical models have allowed for advances made in the artificial pancreases, which are capable of transforming the way diabetes is treated.

2.2. Linear Models and Early Modelling Approaches

One of the earliest studies to have a significant impact on modelling the glucose regulatory system was that of Bolie (1961), who developed a linear model to capture the dynamics between glucose and its regulatory hormone insulin within a healthy subject.

The model was designed to capture the average response of the glucose regulatory system to glucose and insulin. The model consisted of a system of two differential equations, one to represent plasma glucose, the other for plasma insulin:

$$\frac{dx}{dt} = -\alpha x(t) + \beta y(t); \qquad (2.1)$$

$$\frac{dy}{dt} = -\gamma x(t) - \delta y(t); \qquad (2.2)$$

The system assumes a linear relationship between the terms in the model, where x(t) and y(t) represent the differences between the concentrations, at time t, and the resting values of both plasma insulin and glucose respectively. Table 2.1 lists the primary definitions of the variables and coefficients in the model, as specified by Bolie.

Table 2.1. Bolie's Model Nomenclature

Symbol	Meaning	Dimension
x	The difference between the extracellular insulin concentration and the mean physiological value of extracellular insulin	Units/litre
y	The difference between the extracellular glucose concentration and the mean physiological value of extracellular glucose	Grams/litre
p	Rate of insulin injection of the volume of the extracellular fluid	Units/hour/litre
q	Rate of glucose injection of the volume of the extracellular fluid	Grams/hour/litre
α	Rate of insulin destruction	Units/hour
β	Rate of insulin production	Units/hour
γ	Rate of accumulation of glucose in the liver	Grams/hour
δ	Rate of tissue utilization of glucose	Grams/hour

Following the work of Bolie, Ackerman et al. (1965) continued developments in modelling the glucose regulatory system, introducing a new linearized model to capture the blood glucose response to orally administered glucose. However, linear equations are typically judged as unacceptable in glucose modelling due to the fact that they provide poor fits to experimental data (Li and Kuang, 2001) and cannot account for the diverse and complicated dynamics that constitute biological processes such as those involved in glucose-insulin kinetics. Sorensen (1985) criticised the work of the likes of Bolie and Ackerman for their oversimplification, particularly in regard to the assumption that the blood glucose response to insulin is proportional to the amount of insulin in the plasma.

Despite its drawbacks, linear models have been commended for their simplistic approach to modelling and for providing the foundation on which many other acknowledged researchers in glucose regulation modelling would go on to base their work (Sulston et al, 2006).

2.3. The Minimal Model

The most frequently modelled scenario is of a glucose tolerance test (GTT), as described in the previous chapter. Considered as a major breakthrough in diabetes modelling (Ajmera et al., 2013), the Minimal Model was developed to describe the glucose-insulin dynamics following an intravenous glucose tolerance test (IVGTT). Since its development, the model has become the most widely accepted and frequently used within physiological research on glucose metabolism (De Gaetano and Arino, 2000).

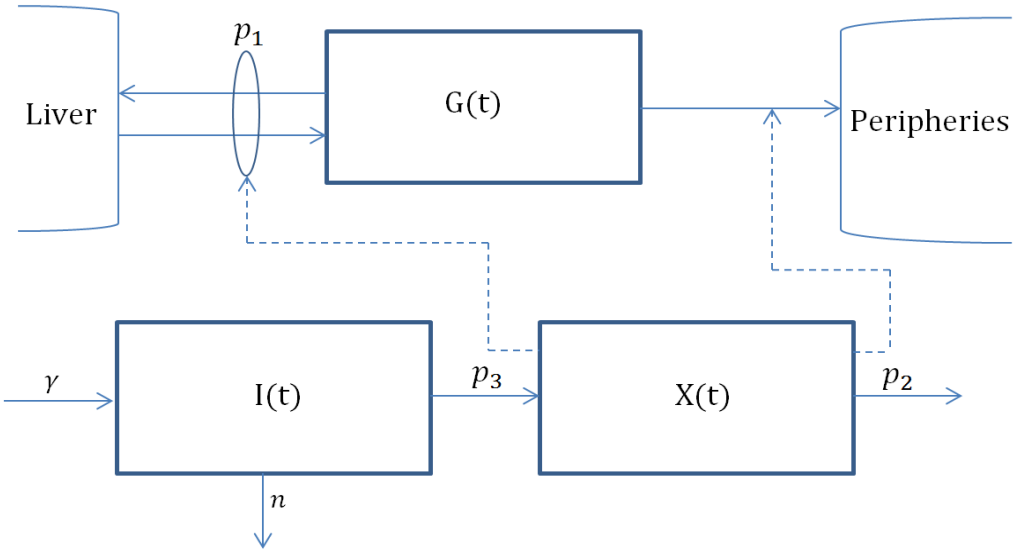


Figure 2.2: Compartmental Diagram of the Minimal Model

Developed by Bergman et al. (1979) the minimal model consists of three compartments, one for the plasma concentrations of both glucose (G) and insulin (I) and one for interstitial insulin activity (X), a compartment introduced to describe the insulin effect on net glucose disappearance (Pacini and Bergman, 1986) .

The original Minimal Model (Bergman et al., 1979) is given as follows:

$$\frac{dG}{dt} = -p_1(G(t) - G_b) - p_4X(t)G(t) - \frac{u_2(t)}{Vol_G}, \qquad (2.3)$$

$$\frac{dX}{dt} = -p_2X(t) + p_3(I(t) - I_b), \qquad (2.4)$$

$$\frac{dI}{dt} = -nI(t) + \gamma(G(t) - h), \qquad (2.5)$$

Subject to the initial conditions

$$\mathrm{G}(0) = G_0, \qquad \mathrm{X}(0) = 0, \qquad I(0) = I_0$$

G_0 and I_0 are treated as unknown parameters, since the model does not account for the glucose intravenously entering the blood stream, but simply assumes plasma glucose and insulin levels have peaked at the start of the test. The model consists of two subsystems; equations (2.3) and (2.4) to model glucose disappearance and equation (2.5) for insulin kinetics.

A description of the variables and parameters is provided in table 2.2.

Table 2.2. Minimal Model Nomenclature

Symbol	Meaning	Dimension
$G(t)$	Plasma glucose concentration at time t	mg/dl
$X(t)$	Interstitial insulin at time t	min^{-1}
$I(t)$	Plasma insulin at time t	$\mu Ul/ml$
G_b	Baseline plasma glucose	mg/dl
I_b	Baseline plasma	$\mu Ul/ml$
p_1	Insulin independent rate of glucose uptake in tissues, often referred to as 'Glucose Effectiveness'	min^{-1}
p_2	Decline in ability of glucose uptake in tissues	min^{-1}
p_3	Increased insulin dependent ability of glucose uptake in tissues	$min^{-2}(\mu Ul/ml)^{-1}$
h	Target glycaemia	mg/dl
γ	Rate of release of insulin in response to excess plasma glucose	$(\mu Ul/ml)$ $(mg/dl)^{-1}min^{-1}$
n	Decay rate for plasma insulin	min^{-1}
$S_I = p_3/p_2$	Insulin sensitivity, p_3/p_2, the increase in the fractional clearance rate of glucose per unit change in the plasma insulin concentration (Bergman et al. 1981)	$min^{-1}/\mu U/ml$
$S_G = p_1$	Glucose effectiveness, p_1	$min^{-1}/mg/dl$

Both the time-courses for plasma glucose and insulin concentrations treat each other as known forcing functions, which are separately estimated by available data (De Gaetano and Arino, 2000). Following the predicted behaviour for plasma insulin (eq. 5) the Minimal Model method provides characteristic parameters for the insulin

responsiveness to glucose (Bergman et al. 1981).The interstitial insulin compartment (eq. 4) conceptualizes the activity of insulin outside of the plasma compartment in the model, for example its role in promoting the uptake of glucose by both hepatic and extra hepatic tissues (Roy and Parker, 2007).

The minimal model has made a positive impact to the study of diabetology and was first model of its kind to capture the parameter values for insulin sensitivity, S_I, and glucose effectiveness, S_G, both which whose numerical value offers an effective insight into the metabolic portrait for an individual.

In spite of its popularity; the Minimal Model does have its drawbacks. It is often criticised for providing poor estimates of the values for the glucose effectiveness and insulin sensitivity (Quon et al., 1994), (Marmarelis and Mitsis, 2014), (McDonald et al., 1999) as a result of its over simplification of glucose physiology (Muniyappa et al., 2008).
Other researchers and experimentalists have also questioned the reliability of some of the physiological assumptions and implications of the model, such as the ability of the pancreas to increase its rate of insulin secretion with time linearly (De Gaetano and Arino, 2000).

An ongoing debate has also arisen on the issue of the model being too simplistic, as it was developed to interpret data, not to take full consideration of the underlying physiological processes involved (Tornøe et al., 2004).

Despite the shortcomings of the model, its simplicity and popularity has meant it has been selected as the basis for many developments and extensions in modelling the glucose regulatory system, involved currently in over 500 studies in the literature and versions are often applied in the development for an artificial pancreas (Magdelaine et al., 2015).

2.4. Recent Studies

Since the pioneering work of Bergman et al. (1979) many models have been developed based on the original Minimal Model.

In 1998 Cobelli and co-workers introduced a model that builds on the work of Bergman et al. (1979) in order to overcome the overestimate of glucose effectiveness and underestimate of insulin sensitivity. To do so the authors presented the 'Two-Compartment Minimal Model', a model that differed from the original Minimal Model by introducing an additional compartment for glucose. This added complexity to the model, as it required the use of Bayesian estimation techniques for some of the new unknown parameters. There is some debate as to whether an additional compartment for glucose is or is not beneficial. Muniyappa et al. (2008) reported an improvement in the results of the Minimal Model, whereas Natalucci et al. (2000) found no significant difference between the ability of the models to detect impaired glucose effectiveness and insulin resistance.

Dalla Man et al. (2004) adapted the minimal model by adding a term to enable the model to consider the rate of appearance of glucose as it is absorbed following oral consumption, based on multiple tracer meal validation studies. The 'Oral Minimal Model' was validated and accepted for its ability to measure the rate of glucose absorption in addition to insulin sensitivity, such that the minimal model can be used to analyse results from an OGTT. However this model did not consider any abnormalities in the system, such as diabetes, which was later addressed by Dalla Man et al. (2006).

Many other adaptions of the Minimal Model have appeared in the literature since its development, including models for exercise (Derouich and Boutayeb, 2002), (Roy and Parker, 2007), statistical adaptations (Andersen and Højbjerre, 2005) and considerations for type 1 diabetes (Fernandez et al. 2009).

2.5. Summary

This section has discussed some of the most influential mathematical models to have been developed and the contributions they have made towards Diabetology. Undoubtedly, the Minimal Model has had the biggest impact on modelling of the glucose regulatory system, due to its simple yet accurate ability to simulate glucose levels and identify an impaired glucose response. Therefore the majority of models introduced in this thesis will be founded on the minimal model.

Chapter 3 Glucagon

3.1. Introduction to the Glucagon-Glucose-Insulin Control Loop

Currently the majority of existing mathematical models are restricted to considering insulin-glucose dynamics (Lehmann et al., 2007) neglecting to take into account the effects of the counter regulatory hormone glucagon. This may be due to the fact that, as discussed in chapter 2, the most frequently modelled scenario is the glucose tolerance test, where the counter-regulatory hormones have a minimal role. Despite the negligible role during a glucose regulatory test, the counter regulatory hormones, such as glucagon, are essential in the fasted state, acting to prevent hypoglycaemia which, if left untreated, can result in health problems, such as: unconsciousness, brain damage and death (Brandt, 1999).

Since the aim of this thesis is to successfully develop a mathematical model that is capable of predicting blood glucose levels during exercise, it is essential that the model includes the effects of counter-regulatory hormones in order to avoid hypoglycaemia. To begin with developing a model capable of simulating scenarios where blood glucose levels are low, a model will be developed to take into account the effects of glucagon on blood glucose regulation. Glucagon has been chosen in favour of the other counter-regulatory hormones (such as epinephrine), as it is considered as a potent regulator of the glucose metabolism in addition to insulin (Aronoff et al., 2004).

The first scenario modelled in this thesis will be the Intravenous Glucose Tolerance Test (IVGTT). An IVGTT has been chosen as the data sets consist of a large number of measurement samples taken at frequent intervals, in addition to the fact that it is already a widely modelled scenario, allowing for validation against other models available in the literature. A model will be chosen based on the model accuracy along with the insight and understanding it offers into the glucose regulatory system.

3.2. Critical Review of Glucagon Models

This section will review the models that have been developed so far in the available literature that include the role of glucagon on glucose homeostasis.

In 2006 Sulston and co-workers developed a model of glucose regulation including its hormonal regulation. The model consisted of three equations, one each for concentrations in the plasma of glucose, insulin and glucagon and was capable of highlighting the importance of the two hormones in maintaining glucose within the narrow desired range. The model was simulated for both healthy and diabetic patients, simulating individuals during short periods without food (60 minutes) and following a meal (based on the term from glucose absorption proposed by Yates and Fletcher (2000)).

Herrero et al. (2013) extended the original minimal model of Bergman et al. (1979) by introducing a new term for glucagon action. The new compartment represents the pharmacodynamics of glucagon and its ability to stimulate glucose production.

The model was developed to be used as a bi-hormonal simulator to be used in an artificial pancreas, which could consider the use of exogenous glucagon as a treatment for hypoglycaemia. An additional term was added to blood glucose to account for glucose absorption from a meal, offering a model more representative of day-day activity in comparison with the minimal model. The model was tested with a bi-hormonal controller and successfully validated against experimental data obtained from the study.

3.3. Model Formulations

This section will detail the development of three mathematical models proposed to describe glucose-insulin-glucagon dynamics during an IVGTT. Each subsection will study the relationships between the compartments proposed and go on to form a set of mathematical equations. The following sections will include a mathematical analysis of the models and simulations against experimental data, in order to determine the accuracy and suitability of the models.

3.3.1. Linear Model

When formulating a mathematical model, the main aim is to develop a model such that the variables relate to the observations of the behaviour and relationships that exist within the physical system being modelled. From a simulation perspective it is desirable that the model is relatively simple allowing for a fast, yet accurate, execution. Therefore the first model proposed, derived in Fitches (2015), consists only of linear relationships between the compartments involved, one each for the concentration in the plasma of glucose, insulin and glucagon. The relationships are shown in figure 3.1., where the dashed lines represent the control signals and the solid lines are the fluxes in the amount of glucose or regulatory hormones in the plasma.

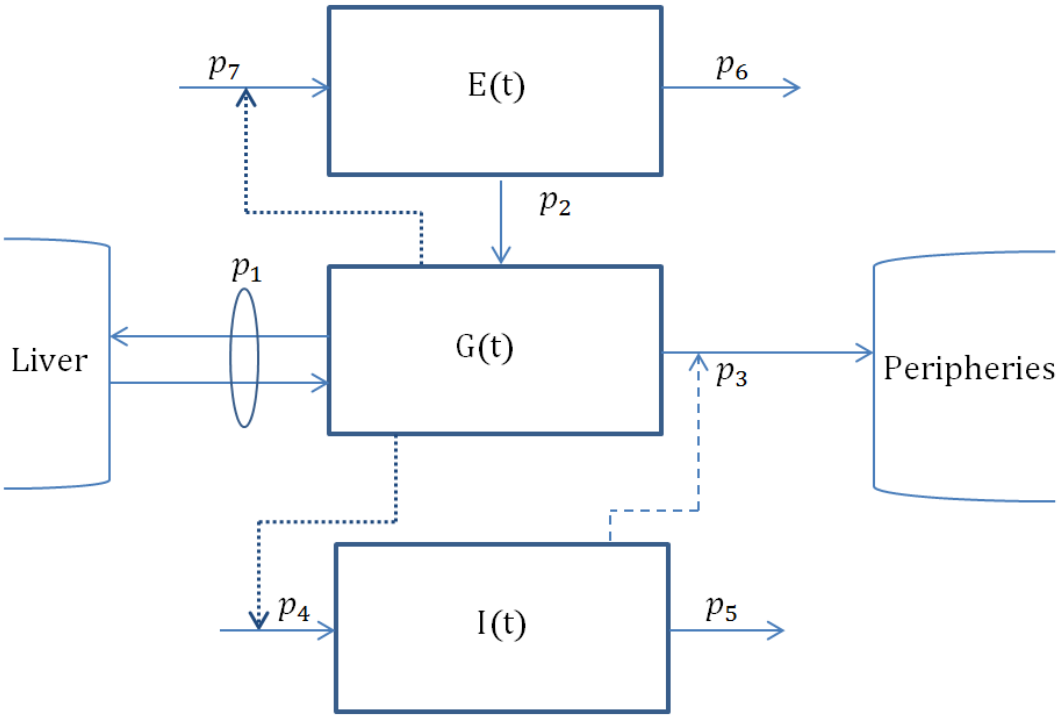


Figure 3.1: Linear bi-hormonal regulation of the glucose regulatory system

In this model glucose levels are considered to be directly affected by the concentrations of insulin and glucagon in the blood, based on the approach by Boilie (1961), and either decrease or increase in a linearly proportional manner to the increase in the concentration of the hormones in the plasma above the corresponding basal levels, $I_b$and E_b.

A description for each rate constant, $p_1 - p_7$, is provided in the following table.

Table 3.1: Linear Glucagon Model Parameter Nomenclature

Parameter	Physiological Description	Unit
p_1	Insulin independent glucose uptake (Glucose effectiveness)	min^{-1}
p_2	Glucagon stimulated glucose production	$(mg/dl)\ min^{-2}$
p_3	Insulin dependent glucose uptake and insulin inhibiting effect on glucose production	min^{-1}
p_4	Glucose stimulated insulin secretion	$(\mu U/ml)\ min^{-2}$
p_5	Insulin production/clearance	min^{-1}
p_6	Glucose stimulated glucagon secretion	$(pg/ml)\ min^{-2}$
p_7	Glucagon production/clearance	min^{-1}

Consequently, the following system of equations for describing an IVGTT is derived:

$$\frac{dG}{dt} = -p_1(G(t) - G_b) + p_2(E(t) - E_b) - p_3(I(t) - I_b), \qquad (3.1)$$

$$\frac{dI}{dt} = p_4(G(t) - G_b)^+ - p_5(I(t) - I_b), \qquad (3.2)$$

$$\frac{dE}{dt} = p_6\big(G_b - G(t)\big)^+ - p_7(E(t) - E_b), \qquad (3.3)$$

Subject to the initial conditions:

$$(0) = G_0, \qquad (0) = I_0, \qquad E(0) = E_b.$$

where G (mg/dl) is the glucose concentration, I (μU/ml) is the insulin concentration and E (pg/ml) is the glucagon concentration, all within the plasma. Both G_0 and I_0 are considered to be unknown parameters, since this model follows the simple approach of the minimal model and, rather than modelling the rate at which glucose enters the plasma from , the model assumes glucose levels to have reached their peak value at the beginning of the test. Since the individual is in the fed state at the start of the test glucagon activity will be supressed; therefore it is assumed that glucagon levels will start

at the basal level, E_b. The positive inflections in equations 3.2 and 3.3 indicate that the terms can only take a positive value; if the term is to become negative it will be set to zero.

Note the system models an individual with a pancreas capable of producing insulin and does not assume T1DM.

This model provides a simple overview of glucose-insulin-glucagon dynamics, which can be solved analytically. However linear models of blood glucose regulation have been criticised for their inability to describe the complex processes that occur, therefore may provide a poor fit to the data. Therefore, a model with non-linear dynamics may be preferable

3.3.2. Glucagon Minimal Model

The Minimal Model was originally designed by Bergman et al. (1979) to analyse the results from an Intravenous Glucose Tolerance Test (IVGTT) and to determine key parameters such as glucose effectiveness and insulin sensitivity. Given that the well-fed condition leads to the secretion of insulin the original minimal model did not include the effects of glucagon, since glucagon secretion is minimal until a couple of hours after the glucose. Since the minimal model is a well-documented model in Diabetology, successfully extending the model for glucagon will develop a model that can be adapted for scenarios of low blood glucose, such as exercise.

A graphical representation of the interactions between compartments in the extended minimal model is given in figure 3.2.

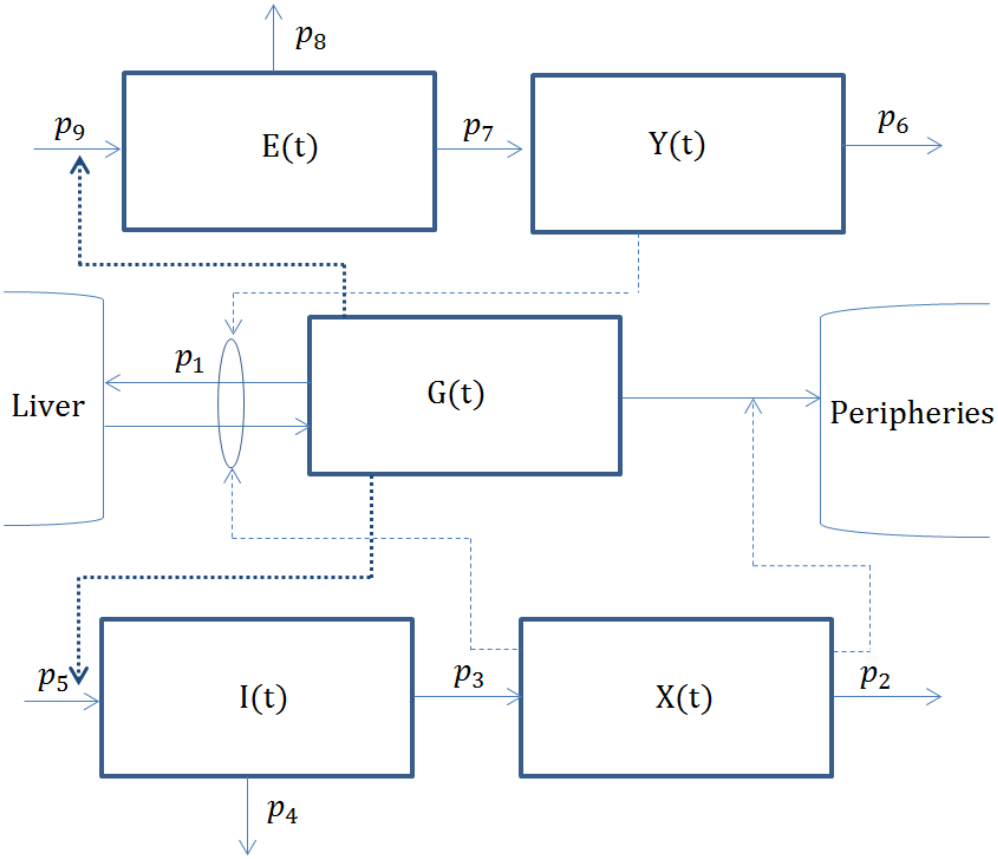


Figure 3.2: Compartment diagram of non-linear bi-hormonal regulation of the glucose regulatory system

The solid lines represent the constant rates, the dark blue dotted lines show signalling of blood glucose levels to the pancreas and the light blue dashed lines show

the control actions on glucose levels. The mathematical description of the parameter rates are described in table 3.2.

Table 3.2. Glucagon Minimal Model Nomenclature

Variable	Description	Unit
G	Plasma glucose concentration	mg/dl
X	Interstitial insulin activity	min^{-1}
I	Plasma insulin concentration	$\mu U/ml$
Y	Glucagon activity	min^{-1}
E	Plasma glucagon concentration	pg/ml
p_1	Glucose Effectiveness	min^{-1}
p_2	Decrease of glucose uptake ability in the peripherals	min^{-1}
p_3	Increase in peripheral glucose uptake ability, proportional to per unit of insulin above baseline	$min^{-2}\,(\mu U/ml)^{-1}$
p_4	Insulin clearance	min^{-1}
p_5	Insulin secretion, proportional to per unit of glucose above baseline	$min^{-2}\,(\mu U/ml)$
p_6	Decrease of glucose production ability in the liver	min^{-1}
p_7	Increase in hepatic glucose production ability, proportional to per unit of glucagon above baseline	$min^{-2}\,(pg/ml)^{-1}$
p_8	Glucagon Clearance	min^{-1}
p_9	Glucagon secretion, proportional to per unit of glucose below baseline	$min^{-2}\,(pg/ml)$

Thus a system of equations, adapted from Fitches (2015), for the model is introduced.

$$\frac{dG}{dt} = -p_1(G(t) - G_b) + G(t)\big(Y(t) - X(t)\big), \quad (3.4)$$

$$\frac{dX}{dt} = -p_2X(t) + p_3(I(t) - I_b)^+, \quad (3.5)$$

$$\frac{dI}{dt} = -p_4(I(t) - I_b) + p_5(G(t) - G_b)^+t, \quad (3.6)$$

$$\frac{dY}{dt} = -p_6Y(t) + p_7(E(t) - E_b)^+, \quad (3.7)$$

$$\frac{dE}{dt} = -p_8(E(t) - E_b) + p_9\big(G_b - G(t)\big)^+t, \quad (3.8)$$

Subject to the following initial conditions:

$$(0) = {}_0, \qquad X(0) = 0, \qquad I(0) = I_0 \qquad Y(0) = 0 \qquad E(0) = E_b$$

Where Y represents the glucagon activity on the liver, X represents the interstitial insulin activity and G, I and E are the quantities of glucose, insulin and glucagon in the plasma. Note $E(0) = E_b$ since both the initial insulin and glucose levels are high; therefore would inhibit excess glucagon production, so glucagon is assumed to be at the resting concentration at the beginning of the test.

This model has increased complexity in comparison with the linear model, however is still relatively simple and minimalistic with respect to the terms used to describe the glucose regulatory processes. The added complexity comes from the non-linear terms introduced into equation (3.4) to model the effects of the regulatory hormones on blood glucose through insulin in the interstitial space and glucagon action, rather than directly by the concentrations of the hormones themselves. Since the role of glucagon in an IVGTT is relatively small, the next model will investigate the effects on assuming the change in blood glucose levels to be linear proportional to the amount of glucagon in the blood, whilst maintaining non- linear glucose-insulin dynamics.

3.3.3. Linear Glucagon Minimal Model

For the third system developed for modelling glucose-insulin-glucagon dynamics during an IVGTT, the term for cellular glucagon, (t), will be removed, assuming that glucose production in response to an excess of glucagon is linearly proportional to the rise in plasma glucagon above the basal level.

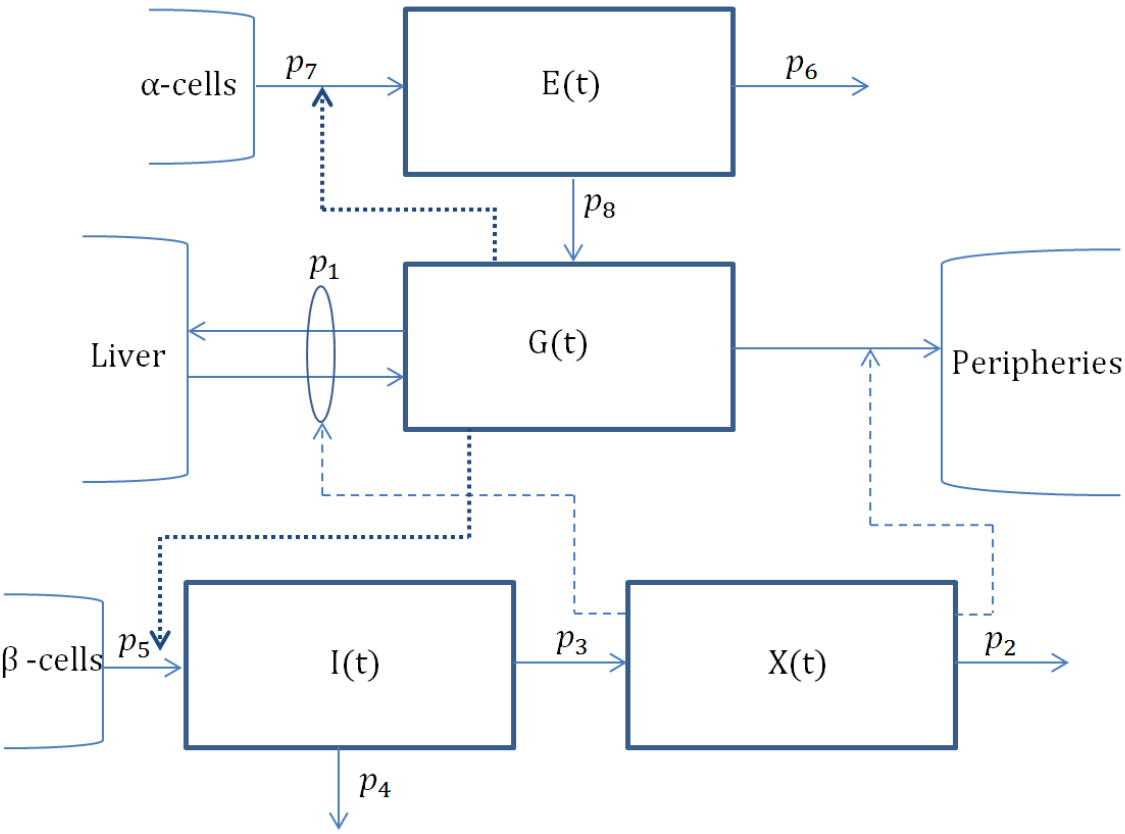


Figure 3.3: Compartment diagram of non-linear insulin and linear glucagon regulation of the glucose regulatory system

The solid lines represent the constant rates, the dark blue dotted lines show signalling of blood glucose levels to the pancreas and the light blue dashed lines show the control actions on glucose levels. The mathematical description of the parameter rates are described in table 3.3.

Table 3.3. Linear Glucagon Minimal Model Nomenclature

Variable	Description	Unit
G	Plasma glucose concentration	mg/dl
X	Interstitial insulin activity	min^{-1}
I	Plasma insulin concentration	$\mu U/ml$
Y	Glucagon activity	min^{-1}
E	Plasma glucagon concentration	pg/ml
p_1	Glucose Effectiveness	min^{-1}
p_2	Decrease of glucose uptake ability in the peripherals	min^{-1}
p_3	Increase in peripheral glucose uptake ability, proportional to per unit of insulin above baseline	$min^{-2}\,(\mu U/ml)^{-1}$
p_4	Insulin clearance	min^{-1}
p_5	Insulin secretion, proportional to per unit of glucose above baseline	$min^{-2}\,(\mu U/ml)$
p_6	Glucagon Clearance	min^{-1}
p_7	Glucagon secretion, proportional to per unit of glucose below baseline	$min^{-2}\,(pg/ml)$
p_8	Glucagon stimulated glucose production	$(mg/dl)\,min^{-2}$

The system of equations is given mathematically as:

$$\frac{dG}{dt} = -p_1(G(t) - G_b) - G(t)X(t) + p_8(E(t) - E_b), \quad (3.9)$$

$$\frac{dX}{dt} = -p_2X(t) + p_3(I(t) - I_b)^+, \quad (3.10)$$

$$\frac{dI}{dt} = -p_4(I(t) - I_b) + p_5(G(t) - G_b)^+t, \quad (3.11)$$

$$\frac{dE}{dt} = -p_6(E(t) - E_b) + p_7\big(G_b - G(t)\big)^+t, \quad (3.12)$$

Subject to the following initial conditions:

$$(0) = G_0, \;\; (0) = 0, \;\; I(0) = I_0, \;\; E(0) = \;\; E_b.$$

3.4. Model Analyses

This section will analyse the three models proposed mathematically, determining the critical points of the systems and reviewing the stability.

3.4.1. Linear Model

An autonomous differential equation is an equation in which the independent variable does not appear explicitly (Zill, 2013). Therefore, if it is the independent variable, a first-order differential equation may be written in normal form as $\frac{dy}{dt} = f(y)$.

To find the critical points of the linear model, equations (3.1-3.3) can be set to be equal to 0 and may be rewritten to give the following:

$$G^* = G_b + \frac{p_2}{p_1} * (E^* - E_b)^+ - \frac{p_3}{p_1}(I^* - I_b)^+, \quad (3.13)$$

$$I^* = \frac{p_4}{p_5} * (G^* - G_b)^+ + I_{b,} \quad (3.14)$$

$$E^* = \frac{p_6}{p_7} * (G_b - G^*)^+ + E_b, \quad (3.15)$$

Where G^*, I^* and E^* represent the concentrations of glucose, insulin and glucagon at the equilibrium point respectively.

Therefore it can be deduced that

$$\lim_{t\to\infty}(t) = G_b, \ \lim_{t\to\infty} I(t) = I_b \ and \ \lim_{t\to\infty} E(t) = E_b.$$

Resulting in an existing equilibrium point (G_b, I_b, E_b).

This means that after any perturbation to the system, for example a meal containing a large amount of carbohydrates, the system will always return back to its basal state.

The linear model admits one equilibrium point, (G_b,,E_b), such that any solution to the system will converge towards it. Solutions and time derivatives of all three equations are all positive and bounded.

The stability analysis of the linear glucagon model and all later linear or linearized versions of models proposed in the thesis will be determined by the Routh-Hurwitz Critera (see definitions and abbreviations).

One form of stability analysis for linear systems is eigenvalue analysis (DeJesus and Kaufamn, 1987). In order to obtain the eigenvalues for the system, the characteristic equation must be determined, which can be found by the Jacobian matrix. The Jacobian matrix for the linear model is given by:

$$J_0 = \begin{pmatrix} \frac{d^2G(t)}{dtdG} & \frac{d^2G(t)}{dtdI} & \frac{d^2G(t)}{dtdE} \\ \frac{d^2I(t)}{dtdG} & \frac{d^2I(t)}{dtdI} & \frac{d^2I(t)}{dtdE} \\ \frac{d^2E(t)}{dtdG} & \frac{d^2E(t)}{dtdI} & \frac{d^2E(t)}{dtdE} \end{pmatrix} = \begin{pmatrix} -p_1 & -p_3 & p_2 \\ p_4 & -p_5 & 0 \\ -p_6 & 0 & -p_7 \end{pmatrix} \quad (3.16)$$

Which can be written in the form of (3.17) as:

$$(\lambda I - J_0) = \begin{pmatrix} \lambda + p_1 & -p_3 & -p_2 \\ -p_4 & \lambda + p_5 & 0 \\ -p_6 & 0 & \lambda + p_7 \end{pmatrix} \quad (3.17)$$

Thus the characteristic polynomial is:

$$p(\lambda) = \lambda^3 + \lambda^2(p_7 + p_5 + p_1) + \lambda(p_1p_5 + p_1p_7 + p_5p_7 - p_3p_4 - p_2p_6) - p_2p_5p_6 + p_1p_5p_7 - p_3p_4p_7 = 0, \quad (3.18)$$

The roots were determined using the Roots function in Mathematica, an example of which can be found in Appendix C. The roots will not be written explicitly in this thesis due to the complexity and length of the values, however it is noted that these values are all negative, thus the stability criteria for the linear model holds.

3.4.2. Glucagon Minimal Model

In mathematical analysis, non-dimensionalizing, or rescaling, is performed in order to simplify the equations by reducing the number of variables in the system, analyse the system behaviour with no regard to the units and to rescale the parameters and variables such that all quantities are of similar magnitudes (De Pillis, 2005). The simplified equations result in fewer parameters. This process reveals the dependence of the system on parameters or groups of parameters.

In this section the glucagon Minimal Model will be non-dimensionalized in order to investigate the behaviour of the system.

Table 3.4 consists of both the state variables and parameters in the system, defining their meanings, range of measurements in the specified units and their corresponding dimensions, given in the fundamental units; Mass (M), length (L) and time (T).

Table 3.4: Values, units and dimensions of variables and parameters in the Glucagon Minimal Model

Symbol	Description	Unit	Dimension		
			M	L	T
G(t)	*Plasma Glucose concentration at time t*	$mg/dl\ (mg/L^{-1})$	1	-3	0
I(t)	*Plasma Insulin concentration at time t*	$\mu U/ml$	1	-3	0
X(t)	*Interstitial Insulin activity at time t*	min^{-1}	0	0	-1
Y(t)	*Glucagon activity at time t*	min^{-1}	0	0	-1
E(t)	*Plasma Glucagon concentration at time t*	pg/ml	1	-3	0
p_1	*Glucose Effectiveness*	min^{-1}	0	0	-1
p_2	*Rate of tissue glucose uptake ability*	min^{-1}	0	0	-1
p_3	*Rate of excess plasma insulin stimulated insulin activity*	$min^{-2}\ (\mu U/ml)^{-1}$	-1	3	-2
p_4	*Insulin disappearance*	min^{-1}	0	0	-1
p_5	*Rate of second phase insulin secretion (glucose dependent)*	$(\mu U/ml)\ min^{-2}$	1	3	-2
p_6	*Rate of cellular glucose production ability*	min^{-1}	0	0	-1
p_7	*Rate of excess plasma glucagon stimulated glucagon activity*	$(pg/ml)\ min^{-2}$	1	3	-2
p_8	*Glucagon clearance*	min^{-1}	0	0	-1
p_9	*Glucose dependent Glucagon secretion*	$(mg/dL)\ min^{-2}$	0	0	-2
G_b	*Baseline plasma glucose concentration*	mg/dl	1	-3	0
I_b	*Baseline plasma insulin concentration*	$\mu U/ml$	1	-3	0
$E_0 = E_b$	*Baseline plasma glucagon concentration*	ng/dl	1	-3	0
G_0	*Initial plasma glucose concentration*	mg/dl	1	-3	0
I_0	*Initial plasma insulin concentration*	$\mu U/ml$	1	-3	0

Therefore in total there are 5 variables (G, X, I, E, Y) and 14 parameters ($p_1, p_2, p_3, p_4, p_5, p_6, p_7, p_8, p_9, G_b, I_b, E_b, G_0, and\ I_0$), giving the system a total of 19 quantities, in 3 fundamental dimension units, and a degree of freedom (DOF) of 11, as determined by the Buckingham π theorem taken from Van Groesen and Molenaar (2007).

Since there are more than 4 variables and only 3 dimensional quantities, a unique relation between the variables cannot be found. Therefore we are required to refer to dimensionless groups of variables, in this case 2 dimensionless groups (number of variables – numbers of dimensions).

There is no unique definition for the procedure of constructing a set of dimensionless quantities, however it is beneficial to formulate a set that is meaningful, that simplifies the equations (Nittala et al, 2006) and aims to reduce the number of parameters (Van Groesen and Molenaar, 2007).

Therefore an optimal scaling for the plasma concentrations for glucose and the two hormones would be $\tilde{G} = \frac{G}{G_b}, \tilde{X} = X\tau, \tilde{I} = \frac{I}{I_b}, \tilde{\mathrm{Y}} = \mathrm{Y}\tau$ and $\tilde{E} = \frac{E}{E_b}$.

The rescaling of variables is chosen to simplify the equations, therefore the baseline values were chosen for chose the three measurable quantities, whereas interstitial insulin and glucagon activity were rescaled by time, consistently with the work of Nittala et al. (2006).

Since interstitial insulin and glucagon activity cannot be measured like the other three state variables, they need to be solved. Therefore, the equation can be rearranged and solved by the integrating factor method as follows.

Rewriting the equations (3.17) and (3.19) for interstitial insulin into the form

$$\frac{dy}{dt} + (t) * (t) = f(t), \tag{3.19}$$

Gives the following

$$\frac{dX}{dt} + p_2 * X(t) = p_3 * (I(t) - I_b), \tag{3.20}$$

$$\frac{dY}{dt} + p_6 * Y(t) = p_7 * (E(t) - E_b), \tag{3.21}$$

Setting the integrating factors, $m_X(t)\ and\ m_y(t)$, as

$$m_x(t) = e^{(p_2 \int dt)} = e^{p_2 t}, \tag{3.22}$$

$$m_y(t) = e^{(p_6 \int dt)} = e^{p_6 t}, \tag{3.23}$$

The integrating factors are then substituted into the formula (Munkhammar, no date).

$$y(t) = \frac{1}{m(t)} * (\int m(t) * f(t) dt), \tag{3.24}$$

Resulting in the following solutions for insulin and glucagon activity

$$X(t) = e^{-p_2 t} * \left(p_3 * \int_0^t e^{p_2 \tau} * (I(\tau) - I_b) d\tau\right), \tag{3.25}$$

$$Y(t) = e^{-p_6 t} * \left(p_7 * \int_0^t e^{p_6 \tau} * (E(\tau) - E_b) d\tau\right), \tag{3.26}$$

Since this model has been developed to analyse the results of a frequently sampled intravenous tolerance test (FSIVGTT) it can be assumed that $X(0) = Y(0) = 0$, as it is assumed that the test is started when the individual is in the basal state.

The dimensional variables are rescaled to give the following dimensionless variables:

$$t = \tau * T, G = \widetilde{G} * G_b, I = \tilde{I} * I_b, E = \tilde{E} * E_b\ and\ X = \frac{\tilde{X}}{\tau}$$

Given that $\frac{d}{dt} = \frac{d}{dT} \rightarrow \frac{dT}{dt} = \frac{1}{\tau} * \frac{d}{dT}$, by replacing the variables in the original system (equations 5.10 – 5.13) with the new variables, the system can now be rewritten in dimensionless form as:

$$\frac{d\tilde{G}}{dt} = -p_1 * \tau * \left(\tilde{G} - 1\right) - \tilde{G} * \left(\tilde{I} - \tilde{Y}\right), \tag{3.27}$$

$$\frac{d\tilde{X}}{dt} = -p_2 * \tau * \tilde{X} + p_3 * \tau^2 * I_b * (\tilde{I} - 1)^+, \tag{3.28}$$

$$\frac{d\tilde{I}}{dt} = -p_4 * \tau * (\tilde{I} - 1) + \frac{p_5 * G_b * \tau^2 * \left(\tilde{G} - 1\right)^+}{I_b}, \tag{3.29}$$

$$\frac{d\tilde{Y}}{dt} = -p_6 * \tau * \tilde{Y} + p_7 * \tau^2 * E_b * \left(\tilde{E} - 1\right)^+, \tag{3.30}$$

$$\frac{d\tilde{E}}{dt} = -p_8 * \tau * \left(\tilde{E} - 1\right) + \frac{p_9 * G_b * \tau^2 * \left(1 - \tilde{G}\right)^+}{E_b}, \tag{3.31}$$

Nittala et al. (2006) identify the two natural time scales in the minimal model used for the FSIVGTT to be glucose disappearance, $\frac{1}{p_1}$, and insulin disappearance, $\frac{1}{p_4}$. This suggests that from the addition of glucagon into this model there is a third time scaled to be considered in this model as glucagon disappearance, $\frac{1}{p_8}$.

Therefore, by using glucagon disappearance to rescale the tie variable such that $\tau = p_8 t$, the system now becomes:

$$\frac{d\tilde{G}}{dt} = -\widetilde{p_1} * \left(\tilde{G} - 1\right) + (\tilde{Y} - \tilde{X}) * \tilde{G}, \tag{3.32}$$

$$\frac{d\tilde{X}}{dt} = -\widetilde{p_2} * \tilde{X} + p_{\tilde{3}} * (\tilde{I} - 1)^{+}, \tag{3.33}$$

$$\frac{d\tilde{I}}{dt} = -\widetilde{p_4} * (\tilde{I} - 1) + \widetilde{p_5} * \left(\tilde{G} - 1\right)^{+}, \tag{3.34}$$

$$\frac{d\tilde{Y}}{dt} = -\widetilde{p_6} * \tilde{Y} + \widetilde{p_7} * \left(\tilde{E} - 1\right)^{+}, \tag{3.35}$$

$$\frac{d\tilde{E}}{dt} = -\left(\tilde{E} - 1\right) + \widetilde{p_9} * \left(1 - \tilde{G}\right)^{+}, \tag{3.36}$$

where $\tilde{G} = \frac{G}{G_b}, \tilde{I} = \frac{I}{I_b}, \tilde{E} = \frac{E}{E_b}, \widetilde{p_1} = \frac{p_1}{p_8}, \widetilde{p_2} = \frac{p_2}{p_8}, \widetilde{p_3} = \frac{p_3 * I_b}{p_8^2}, \widetilde{p_4} = \frac{p_4}{p_8}, \widetilde{p_5} = \frac{p_5 * G_b}{p_{8^2} * I_b}, \widetilde{p_6} = \frac{p_6}{p_8}, \widetilde{p_7} = \frac{p_7 * E_b}{p_8^2}$ and $\widetilde{p_9} = \frac{p_9 * G_b}{p_8^2 * E_b}$. The initial conditions become: $\tilde{G}(0) = \frac{G_0}{G_b}$, $\tilde{\mathrm{X}}(0) = 0, \tilde{I}(0) = \frac{I_0}{I_b}. \tilde{Y} = 0$ and $\tilde{E} = \frac{E_b}{E_b} = 1$.

Therefore the free, unitless parameters comprise of: $\widetilde{p_1}, \widetilde{p_2}, \widetilde{p_3}, \widetilde{p_4}, \widetilde{p_5}, \widetilde{p_6}, \widetilde{p_7}, \widetilde{p_9}, \widetilde{G_0}$ and $\widetilde{I_0}$. This indicates a DOF of 10, rather than 11 as given by the Buckingham-π theorem, however this quantity is one less due to the assumption that $E_0 = E_b$.

The key parameters now change to $\widetilde{S_G} = \widetilde{p_1} = \frac{p_1}{p_8}, \widetilde{S_I} = \frac{\widetilde{p_3}}{\widetilde{p_2}} = \frac{p_3 I_b}{p_2 p8}$ *and* $\widetilde{S_E} = \frac{\widetilde{p_7}}{\widetilde{p_6}} = \frac{p_7 E_b}{p_6 p_8}$.

Glucose effectiveness now becomes glucose disappearance over glucose independent glucagon production, insulin sensitivity now is dependent on insulin sensitivity, basal insulin secretion and glucagon clearance, and the glucagon sensitivity index is now influenced by basal glucagon and glucose independent production.

In order to ensure that the system is autonomous, it can clearly be seen that the critical point must be (1,0,1,0,1). This refers to when the system is in a resting state, i.e. plasma glucose and hormone concentrations are at their basal levels.

In order to determine the stability of the system, the linearized system, given by equations (3.32)-(3.36), is analysed.

The Jacobian Matrix evaluated at the critical point (1,0,1,0,1), is given by:

$$J_1 = \begin{pmatrix} -\tilde{p_1} & -1 & 0 & 1 & 0 \\ 0 & -\tilde{p_2} & \tilde{p_3} & 0 & 0 \\ 0 & 0 & -\tilde{p_4} & 0 & 0 \\ 0 & 0 & 0 & -\tilde{p_6} & \tilde{p_7} \\ 0 & 0 & 0 & 0 & -\tilde{p_8} \end{pmatrix} \tag{3.37}$$

Since J_1 is an upper triangular matrix, the eigenvalues are given by the entries on its main diagonal and are:

$\lambda_{1,1} = -p_1, \lambda_{1,2} = -p_2, \lambda_{1,3} = -p_4, \lambda_{1,4} = -p_6, \lambda_{1,5} = -p_8$

Note that all roots of the characteristic equation are negative, therefore the system is stable.

3.4.3. Linear Glucagon Minimal Model

In this section the third model formulated to consider glucose-insulin-glucagon dynamics in an IVGTT is non-dimensionalized, in a similar manner to the Glucagon Minimal Model in section 3.4.2, in order to investigate the behaviour of the system. Non-dimensionalizing the system will enable the system to be described with fewer parameters by transforming the variables and parameters to simplify the equations. The process reveals the dependence of the system on parameters or groups of parameters.

The following table consists of both the state variables and parameters in the system, defining their meanings, range of measurements in the specified units and their corresponding dimensions, given in the fundamental units; Mass (M), length (L) and time (T).

Table 3.5: Values, units and dimensions of variables and parameters in the Linear Glucagon Minimal Model.

Symbol	Description	Unit	Dimension		
			M	**L**	**T**
G(t)	*Plasma Glucose concentration at time t*	mg/dl	1	-3	0
I(t)	*Plasma Insulin concentration at time t*	$\mu U/ml$	1	-3	0
X(t)	*Interstitial Insulin activity at time t*	min^{-1}	0	0	-1
E(t)	*Plasma Glucagon concentration at time t*	pg/ml	1	-3	0
p_1	*Glucose Effectiveness*	min^{-1}	0	0	-1
p_2	*Decrease of tissue glucose uptake ability*	min^{-1}	0	0	-1
p_3	*Insulin dependent tissue glucose uptake ability*	$min^{-2}\,(\mu U/ml)^{-1}$	-1	3	-2
p_4	*Rate of*	$(\mu U/ml)\,min^{-2}$	0	0	-2
p_5	*Insulin disappearance*	min^{-1}	0	0	-1
p_6	*Glucose dependent Glucagon secretion*	$(pg/ml)\,min^{-2}$	0	0	-2
p_7	*Glucagon clearance*	min^{-1}	0	0	-1
p_8	*Glucagon dependent glucose secretion*	$(pg/ml)\,min^{-2}$	0	0	-2
G_b	*Baseline plasma glucose concentration*	mg/dl	1	-3	0
I_b	*Baseline plasma insulin concentration*	$\mu U/ml$	1	-3	0
$E_0 = E_b$	*Baseline plasma glucagon concentration*	pg/ml	1	-3	0
G_0	*Initial plasma glucose concentration*	mg/dl	1	-3	0
I_0	*Initial plasma insulin concentration*	$\mu U/ml$	1	-3	0

In total there are 4 variables (G, X, I, E) and 13 parameters ($p_1, p_2, p_3, p_4, p_5, p_6, p_7, p_8, G_b, I_b, E_b, G_0, and\ I_0$), giving the system a total of 17 quantities, in 3 fundamental dimension units, and a DOF of 10. From the π-theorem of Buckingham (Van Groesen and Molenaar, 2007) it can be determined that the system can be described with 14 dimensionless quantities:

$$(\mathrm{G}, \mathrm{X}, \mathrm{I}, \mathrm{E}, p_1, p_2, p_3, p_4, p_5, p_6, p_7, p_8, G_b, I_b, E_b, G_0, I_0) \tag{3.38}$$

Between the variables and parameters of a mathematical model can be replaced with the corresponding relation between the dimensionless quantities q_i:

$$f^*(q_1, \dots\dots, q_{14}) = 0 \tag{3.39}$$

In section 3.4.2. it was determined that since interstitial insulin and glucagon activity cannot be measured like the other three state variables, they needed to be solved. This model does not include glucagon activity; however the same approach will be required for interstitial insulin, such that it becomes equation (3.20).

The dimensional variables are rescaled to give the following dimensionless variables:

$$t = \tau * T, G = \widetilde{G} * G_b, I = \tilde{I} * I_b, E = \tilde{E} * E_b\ and\ X = \frac{\tilde{X}}{\tau}$$

Given that $\frac{d}{dt} = \frac{d}{dT} \rightarrow \frac{dT}{dt} = \frac{1}{\tau} * \frac{d}{dT}$, by replacing the variables in the original system 5.10 – 5.13) with the new variables, the system can now be rewritten in dimensionless form as:

$$\frac{d\tilde{G}}{dT} = -p_1 * \tau * \left(\tilde{G} - 1\right) - \tilde{X} * \tilde{G} + \frac{p_8 * E_b * \tau}{G_b} * \left(\tilde{E} - 1\right)^+, \tag{3.40}$$

$$\frac{d\tilde{X}}{dT} = -p_2 * \tau * \tilde{X} + p_3 * \tau^2 * I_b * (\tilde{I} - 1)^+, \tag{3.41}$$

$$\frac{d\tilde{I}}{dT} = -p_4 * \tau * (\tilde{I} - 1) + \frac{p_5 * Gb * \tau^2 * T}{I_b} * \left(\tilde{G} - 1\right)^+, \tag{3.42}$$

$$\frac{d\tilde{E}}{dT} = -p_6 * \tau * \left(\tilde{E} - 1\right) + \frac{p_7 * G_b * \tau^2 * T}{E_b} * \left(1 - \tilde{G}\right)^+, \tag{3.43}$$

$$\tilde{G}(0) = \frac{G_0}{G_b} = \widetilde{G_0}, \qquad \tilde{I}(0) = \frac{I_0}{I_b} = \widetilde{I_0}, \qquad \tilde{E}(0) = \frac{E_b}{E_b} = 1, \qquad X(0) = 0.$$

As discussed in section 3.4.2 there are three natural time scales for this system, each for glucose clearance, insulin clearance and glucagon clearance. By setting $\tau = \frac{1}{p_4}$, the system is rescaled for insulin disappearance and can be rewritten as:

$$\frac{d\tilde{G}}{dT} = -\widetilde{p_1} * \left(\tilde{G} - 1\right) - \tilde{X} * \tilde{G} + \widetilde{p_8} * \left(\tilde{E} - 1\right)^{+}, \tag{3.44}$$

$$\frac{d\tilde{X}}{dT} = -\widetilde{p_2} * \tilde{X} + \widetilde{p_3} * (\tilde{I} - 1)^{+}, \tag{3.45}$$

$$\frac{d\tilde{I}}{dT} = -(\tilde{I} - 1) + \widetilde{p_5} * \left(\tilde{G} - 1\right)^{+}, \tag{3.46}$$

$$\frac{d\tilde{E}}{dT} = -\widetilde{p_6} * \left(\tilde{E} - 1\right) + \widetilde{p_7} * \left(1 - \tilde{G}\right)^{+}, \tag{3.47}$$

where the dimensionless parameters are defined as:

$$\widetilde{p_1} = \frac{p_1}{p_4}, \quad \widetilde{p_2} = \frac{p_2}{p_4}, \qquad \widetilde{p_3} = \frac{p_3}{p_4^2} * I_b, \quad \widetilde{p_5} = \frac{p_5 * Gb * T}{I_b * p_4^2}, \qquad \widetilde{p_6} = \frac{p_6}{p_4},$$

$$\widetilde{p_7} = \frac{p_7 * G_b * T}{E_b * p_4^2}, \text{ and } \widetilde{p_8} = \frac{p_8 * E_b}{G_b * p_4}.$$

Therefore the free, unitless parameters comprise of $\widetilde{p_1}$, $\widetilde{p_2}$, $\widetilde{p_3}$, $\widetilde{p_5}$, $\widetilde{p_6}$, $\widetilde{p_7}$, $\widetilde{p_8}$, $\widetilde{G_0}$ *and* $\widetilde{I_0}$. This indicates a DOF of 9, rather than 10 as given by the Buckingham-π theorem, however this quantity is one less due to the assumption that $E_0 = E_b$.

The key parameters now change to $\widetilde{S_G} = \widetilde{p_1}$ *and* $\widetilde{S_I} = \frac{\widetilde{p_3}}{\widetilde{p_2}} = \frac{p_3 I_b}{p_2 p_4}$. Glucose effectiveness now becomes glucose disappearance and insulin clearance and insulin sensitivity now is dependent on insulin sensitivity, basal insulin secretion and glucose independent insulin production.

It can easily be seen that $\tilde{G}(T) = 1$ must be at a critical point to ensure autonomy in the system.

This reduces the remaining equations of the dimensionless system to:

$$\frac{d\tilde{X}}{dT} = -\widetilde{p_2} * \tilde{X} + \widetilde{p_3} * (\tilde{I} - 1)^{+}, \tag{3.48}$$

$$\frac{d\tilde{I}}{dT} = -\widetilde{p_4} * (\tilde{I} - 1), \tag{3.49}$$

$$\frac{d\tilde{E}}{dT} = -\widetilde{p_6} * \left(\tilde{E} - 1\right), \tag{3.50}$$

Therefore it can be determined that the critical point for the dimensionless system must be: $\tilde{G}(T) = 1,\ \tilde{X}(T) = 0,\ \tilde{I}(T) = 1,\ \tilde{E}(T) = 1$. In physical terms this point represents the individual at their basal metabolic rate, i.e. a post-absorptive state at rest and not under any form of physiological or mental stress.

The Jacobian Matrix is evaluated at the critical point for the dimensional system, rescaled for insulin disappearance (3.44-3.47), and given as :

$$= \begin{pmatrix} -\widetilde{p_1} & -1 & 0 & \widetilde{p_8} \\ 0 & -\widetilde{p_2} & \widetilde{p_3} & 0 \\ \widetilde{p_5} & 0 & -\widetilde{p_4} & 0 \\ -\widetilde{p_7} & 0 & 0 & -\widetilde{p_6} \end{pmatrix} \tag{3.51}$$

$$\det(J_2 - I\lambda) = \begin{pmatrix} -\widetilde{p_1} - \lambda & -1 & 0 & \widetilde{p_8} \\ 0 & -\widetilde{p_2} - \lambda & \widetilde{p_3} & 0 \\ \widetilde{p_5} & 0 & -\widetilde{p_4} - \lambda & 0 \\ -\widetilde{p_7} & 0 & 0 & -\widetilde{p_6} - \lambda \end{pmatrix} = 0 \tag{3.52}$$

Using Mathematica, the characteristic equation was calculated as:

$$det(J_2 - I\lambda) = \widetilde{p_7}\left(\widetilde{p_2}^2\widetilde{p_4} + \widetilde{p_2}^2\,\lambda + \widetilde{p_2}\widetilde{p_4}\,x + \widetilde{p_2}\,\lambda^2\right)$$
$$+(\widetilde{p_6} - x)\left(-\widetilde{p_3}\,\widetilde{p_5} + (-\widetilde{p_4} - \lambda)(\widetilde{p_1}\,\widetilde{p_2} + \widetilde{p_1}\,\lambda + \widetilde{p_2}\,\lambda + \lambda^2)\right) = 0 \tag{3.53}$$

The roots of the equation (3.53) were solved in Mathematica to give the eigenvalues for the matrix (3.51). (See appendix C for an example code). The eigenvalues were all negative, confirming the stability of the system.

3.5. Model Simulations

The models are solved using the inbuilt MATLAB solver ODE45, based on explicit Runge-Kutta methods. The value of the parameters are solved within MATLAB using the LSQNONLIN function. Initial parameter values were based on those available within literature (Cobelli et al. 1998), (Roy and Parker, 2007), (McDonald et al., 2000), Aguilera Gonzalez and Darouach, 2015), the LSQNONLIN solver then used these values to determine the optimal set of parameters to fit the data set (table 3.2 found in the appendix) of glucose and insulin measurements obtained during a frequently sampled intravenous glucose tolerance test (FSIVGTT) from a healthy individual (Pacini and Bergman, 1986).

The initial concentrations for plasma glucose and insulin were estimated using starting values and bounds based on Pacini and Bergman's (1986) MINMOD program. Since during a FSIVGTT an individual is considered to be in the fed state, minimal glucagon action is assumed, thus set $E_0 = E_b$. Measurements for basal Insulin, I_b, Glucose, G_b, and Glucagon, E_b, were taken from Wolfe et al. (1986). ($I_b = 13.2 \pm 1.4$ (μU/mL), $G_b = 92.5 \pm 6.09$ (mg/dL) and $E_b = 142 \pm 36$ (pg/mL).) The remaining parameters were constrained with lower and upper bounds based on findings in literature where available. The parameters for the models containing glucagon activity and/or plasma glucagon were calculated based on the starting values for the insulin counterparts; however constraints on the lower and upper bounds were decreased due to the limited information available in literature. Tables with the parameter values can be found in appendix B.

3.5.1. Plasma Glucose

Figure 3.4 shows the ability of all three proposed models to produce an accurate fit to the dataset for plasma glucose measurements. Out of the three models , The Linear Model (a) is the poorest to fit the dataset, as it assumes glucose levels to fall slightly too quickly in the initial ten minutes and shows glucose levels to gradually decline until reaching the basal level. The other two models capture the initial decline and manage to account for plasma glucose undershooting the basal level, which are then restored by glucagon action. It can be seen that The Glucagon Minimal Model (b) provides the most accurate fit.

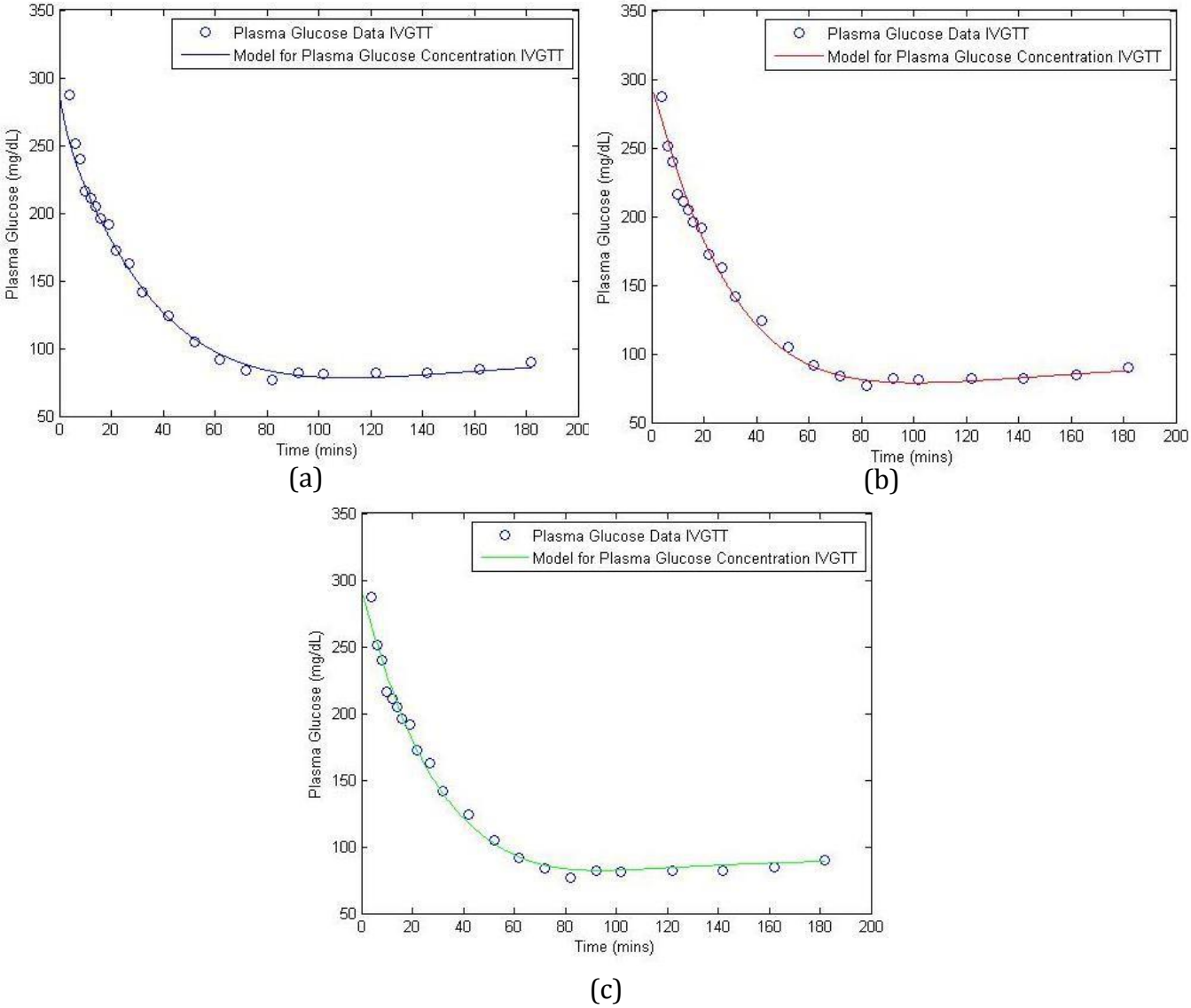
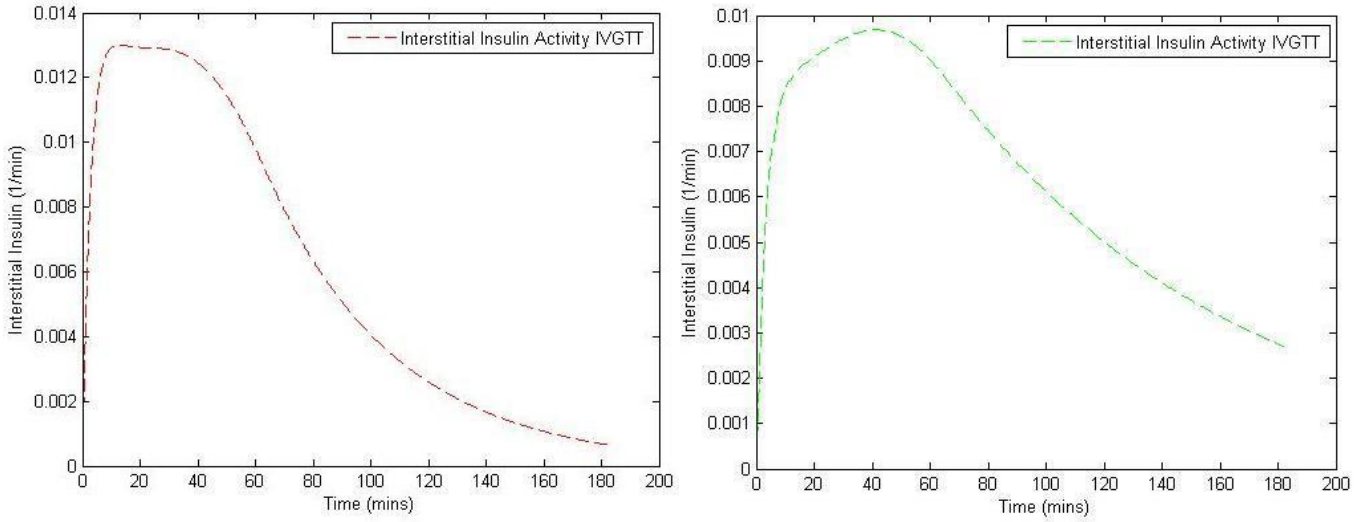


Figure 3.4: Simulations of plasma glucose concentrations during an IVGTT: The Linear Model (a), The Glucagon Minimal Model (b) and The Linear Glucagon Minimal Model (c).

3.5.2. Interstitial Insulin

The predictions for interstitial insulin of both of the models are of a similar magnitude to the Minimal Model and follow the behaviour of insulin. The Glucagon Minimal Model (a) is much faster to reach a peak of insulin activity and is cleared from the system faster than in the Linear Glucagon Minimal Model (b), suggesting a slightly greater sensitivity to insulin.



(a) (b)

Figure 3.5: Simulations of interstitial insulin activity during an IVGTT: The Glucagon Minimal Model (a) and The Linear Glucagon Minimal Model (b).

3.5.3. Plasma Insulin

The Linear Glucagon Model does not capture the biphasic release of insulin, plotting a smooth curve as the insulin concentration returns to the basal level. This result is inadequate for modelling insulin dynamics as it has long been observed that high levels of glucose induce a biphasic release of insulin (Taguchi et al., 1995), (Henquin et al., 2002).

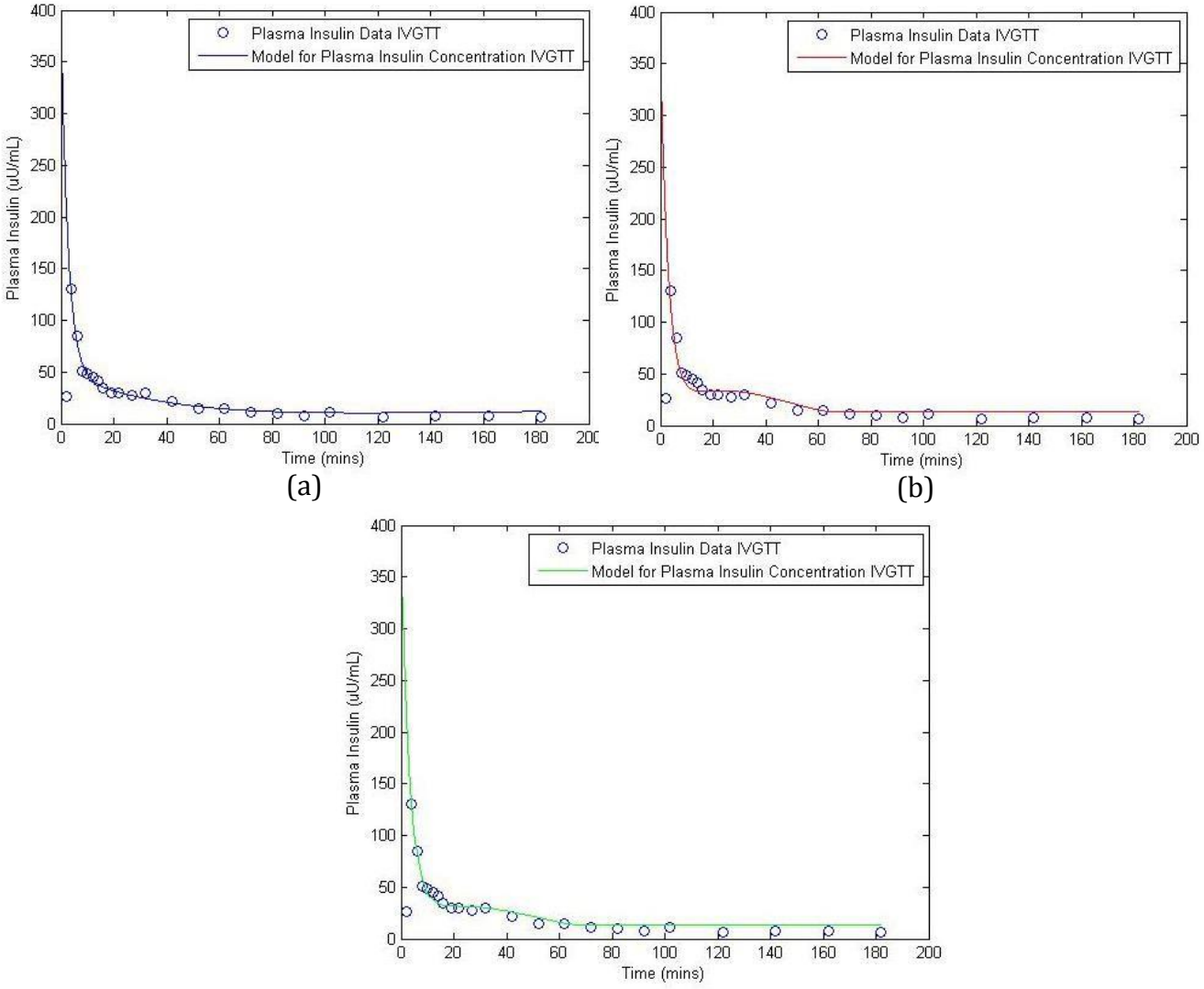


Figure 3.6: Simulations of plasma insulin concentrations during an IVGTT: The Linear Model (a), The Glucagon Minimal Model (b) and The Linear Glucagon Minimal Model (c)

Both the Glucagon Minimal Model (a) and Linear Glucagon Minimal Model (b) fit the data for plasma insulin measurements well and demonstrate the biphasic behaviour as observed for insulin release. These results suggest that linear dynamics are not sufficient for modelling the glucose-insulin relationship.

3.5.4. Glucagon Activity

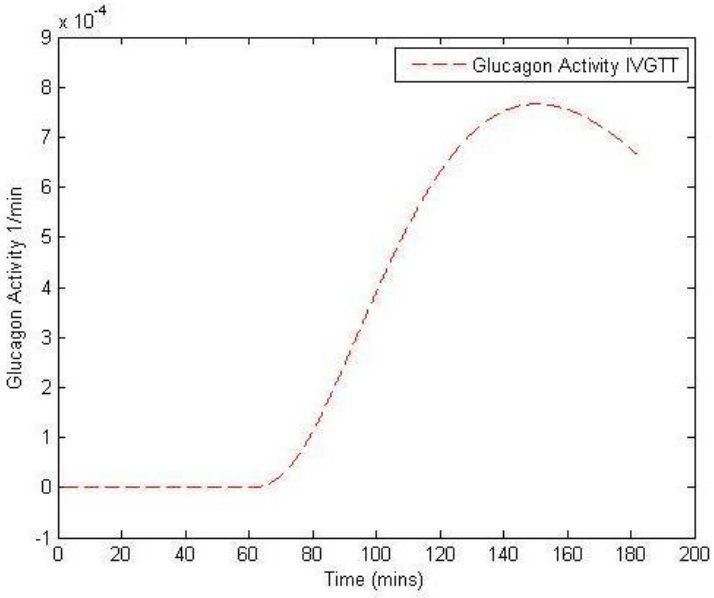


Figure 3.7: Simulation of The Glucagon Minimal Model for glucagon activity during an IVGTT.

The Glucagon Minimal Model is the only model that considers glucagon activity. If it is compared with the results for plasma glucagon for the Glucagon Minimal Model (figure 3.8.b) it is clearly seen that glucagon activity begins to increases after a slight delay of a couple of minutes following the rise in the plasma glucagon concentration. By comparing glucagon activity to interstitial insulin (figure 3.5.a) it is apparent that the level of glucagon activity following a fall in glucose levels is much smaller than the response of interstitial insulin activity to excessive glucose in the initial hour of the test. This result is reasonable due to the magnitude in which glucose exceeded the basal level in comparison to the amount it fell below the basal level.

3.5.5. Plasma Glucagon

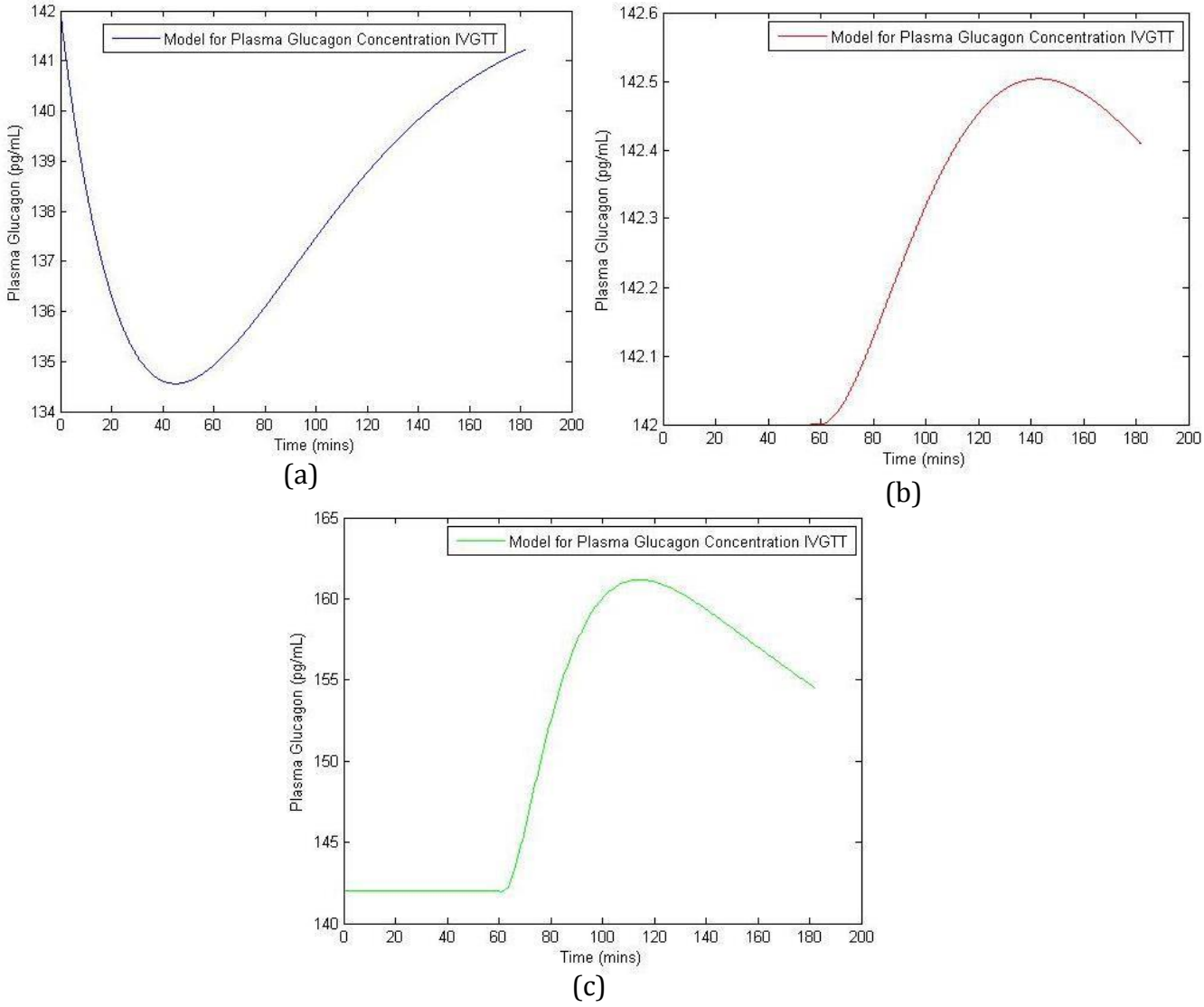


Figure 3.8: Simulations for plasma glucagon concentrations during an IVGTT: The Linear Glucagon Model (a), The Glucagon Minimal Model (b) and The Linear Glucagon Minimal Model (c).

Since the data set used to validate the model did not contain measurements for plasma glucagon, the results have been validated in a more qualitative manner, and compared to the results shown by Thomaseth el at. (2014), in which showed an hour following the IVGTT plasma glucagon concentrations rose by approximately 30% of the basal rate. Clearly the linear model is incapable of predicting such a result, showing plasma glucagon not to rise above the basal level at any point. Both the Glucagon Minimal Model (b) and the Linear Glucagon Model (c) show the expected increase in plasma glucagon concentrations an hour following the intravenous glucose administration. However, the magnitude in which the Glucagon Minimal

Model demonstrates for the increase in glucagon is very minimal, and does not correspond with findings in literature. Therefore the Linear Glucagon Minimal Model is by far the most accurate model in its ability to predict plasma glucagon concentrations during an IVGTT.

3.5.6. Dimensionless Glucagon Minimal Model

The dimensionless system was solved in Matlab using ODE45, with the parameters fitted to the dimensionless data set of Pacini and Bergman (1986). The system was rescaled three times, for each of the recognised time scales; glucose disappearance, insulin disappearance and glucagon disappearance.

The plots in figure 3.**9** show the solutions of the dimensionless model rescaled for glucagon clearance, given by equations (3.33-3.37).

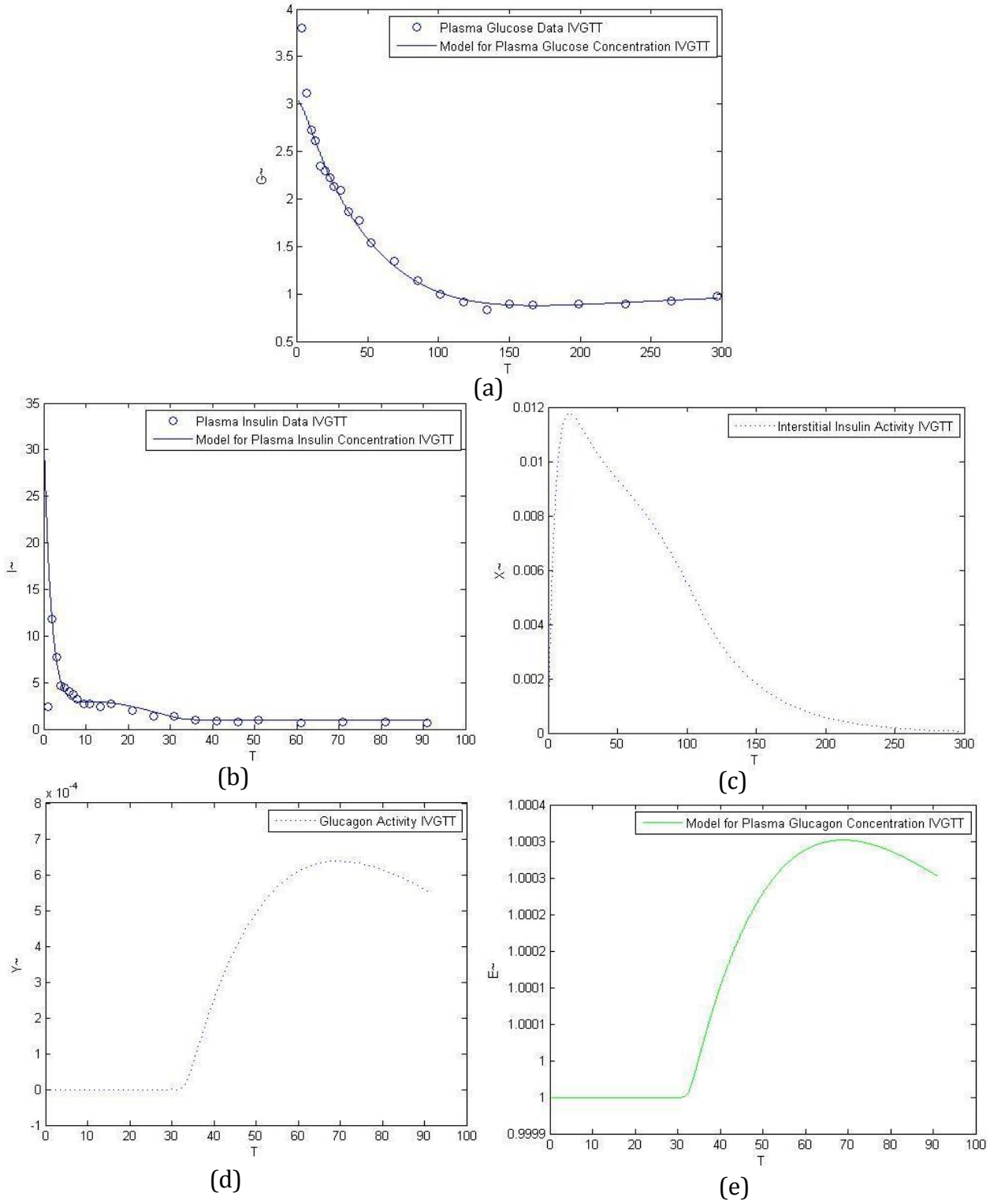


Figure 3.9: Simulations of dimensionless plasma glucose, G(t), against plasma glucose measurements (a), plasma insulin, I(t), against plasma insulin measurements (b), interstitial insulin, X(t), (c), plasma glucagon, E(t), (e) and glucagon activity, Y(t), (d) during an IVGTT. Both data and model have been rescaled for glucagon clearance.

The dimensionless simulation shows similar behaviour to the dimensional model, with both insulin (b) and glucose (a) showing a good fit to the dimensionless data.

The non-dimensional simulation for plasma glucagon (c) highlights the minimal increase in concentrations.

The dimensional parameter values were calculated from the non-dimensional simulation as shown in table 3.**6**.

Table 3.6: Comparisons of parameter values for dimensionless Glucagon Minimal Model, rescaled for glucose clearance, insulin clearance and glucagon clearance.

Parameter	**Dimensional Value**	**Non-Dimensional value rescaled by** $\boldsymbol{\tau = \frac{1}{p_1}}$	**Non-Dimensional value rescaled by** $\boldsymbol{\tau = \frac{1}{p_4}}$	**Non-Dimensional value rescaled by** $\boldsymbol{\tau = \frac{1}{p_8}}$
$S_G = p_1$	0.02058	0.01756659	0.0094137	0.00941386
p_2	0.02218	0.11408124	0.0373353	0.037336576
p_3	0.000014	0.00003604	0.0000201	0.000020156
p_4	0.32	0.03563689	0.2783405	0.278343671
p_5	0.0032	0.00630156	0.0033421	0.003342215
p_6	0.142	1.1440989	0.7025258	0.702525919
p_7	0.000217	0.06857451	0.0079650	0.007964075
p_8	0.0494	0.04687327	0.499999	0.5
p_9	0.000018	0.00153339	0.0000245	0.00001
S_I	0.000617	0.00031591	0.0005399	0.00053928
S_E	0.001528	0.0599379	0.0153990	0.0113
G_0	293	292	279	279
I_0	360	366	360	360

Rescaling the dimensionless model for both insulin clearance and glucagon clearance return similar parameter values for both insulin sensitivity and glucose effectiveness, which are slightly less than the dimensional values, whereas the returned values for glucagon effectiveness are very close to the dimensional value.

In comparison, scaling the model for either glucose clearance results in higher values for both glucose effectiveness and glucagon sensitivity, but lower values for insulin sensitivity than the other two scalings.

3.5.7. Dimensionless Linear Glucagon Minimal Model

The dimensionless system was solved in MATLAB using ODE45, with the parameters fitted to the dimensionless data set of Pacini and Bergman (1986). The system was rescaled three times, for each of the recognised time scales; glucose disappearance, insulin disappearance and glucagon disappearance.

The plots in figure 3.9 show the solutions of the dimensionless model rescaled for insulin clearance, given by equations (3.44-3.47).

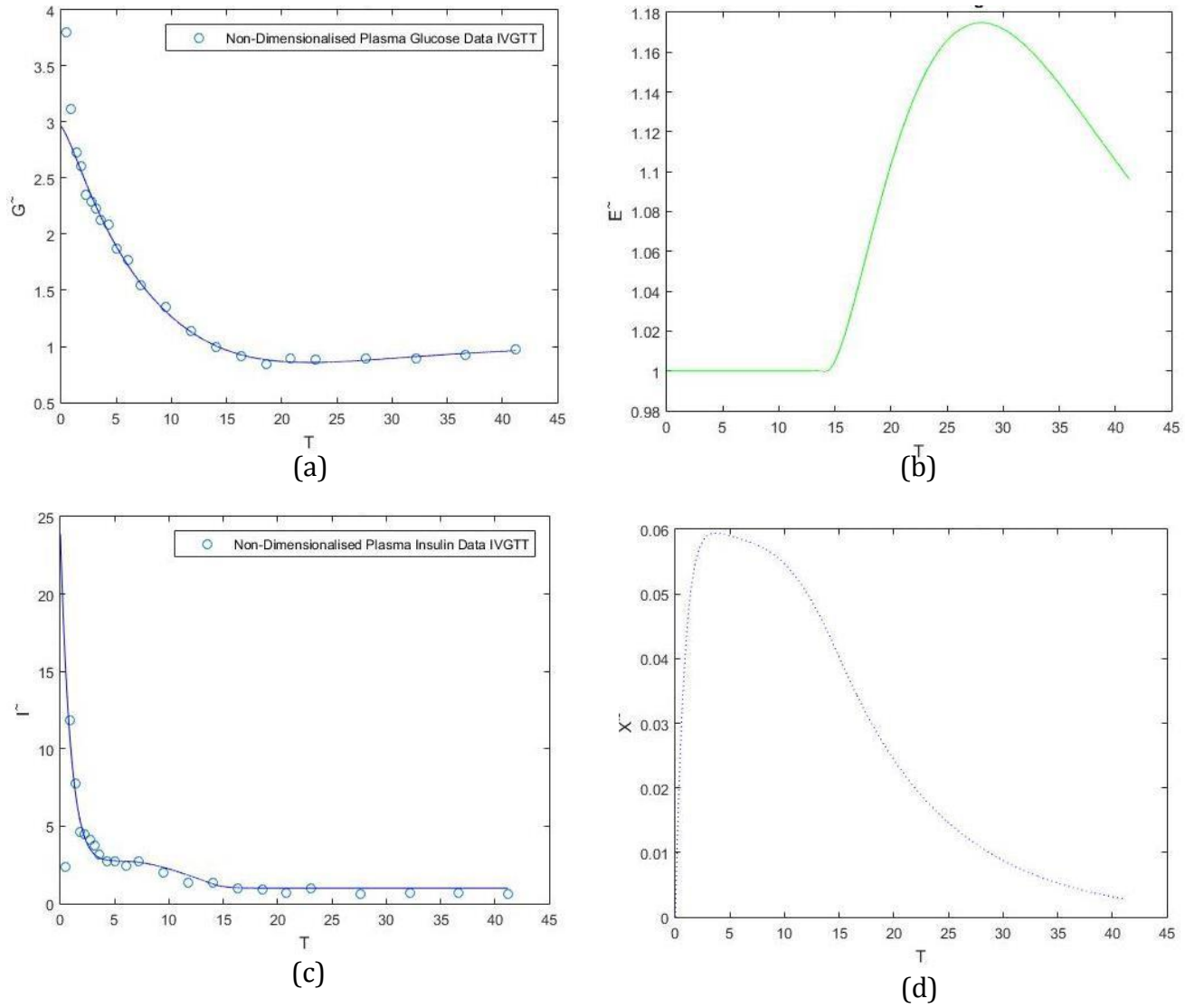


Figure 3.10: Simulations of Linear Glucagon Minimal Model during an IVGTT. The simulations are plotted as follows: Plasma glucose, G(t), against plasma glucose measurements (a), plasma glucagon, E(t), (b).plasma insulin, I(t), against plasma insulin measurements (c), and interstitial insulin activity, X(t), (d).

The model shows a very good fit to the dimensionless data for glucose (a), but rather a poor fit for insulin (c). However the increase in glucagon is as closer to the increase expected based on the findings of Thomaseth et al. (2014), as it increases by almost 20% from its basal value.

Table 3.7: Comparisons of parameter values for dimensionless Linear Glucagon Minimal Model, rescaled for glucose clearance, insulin clearance and glucagon clearance.

Parameter	**Dimensional Value**	**Non-Dimensional value rescaled by $\boldsymbol{\tau = \frac{1}{p_1}}$**	**Non-Dimensional value rescaled by $\boldsymbol{\tau = \frac{1}{p_4}}$**	**Non-Dimensional value rescaled by $\boldsymbol{\tau = \frac{1}{p_6}}$**
$S_G = p_1$	0.02808122	0.01997831	0.0153103	0.0150861
p_2	0.00996122	0.0144932	0.0231139	0.02259839
p_3	$7.31888 * 10^{-6}$	0.0000108854	0.00001459	0.000014613
p_4	0.27943170	0.20202604	0.22646731	0.212060508
p_5	0.00290469	0.00197596	0.0023889	0.002129929
p_6	0.19225742	0.485124233	0.1222461	0.221008791
p_7	0.00364470	0.002605806	0.00124715	0.00152487
p_8	0.01530144	0.037376378	0.0116759	0.01809859
S_I	$7.34737 * 10^{-4}$	0.000751068	0.00063153	0.000646669
G_0	293	282	279	282
I_0	360	411	406	410

Rescaling the dimensionless model for all three parameter values resulted in lower values for glucose effectiveness, whereas the values for insulin sensitivity did not vary much. Interestingly, the starting values were all considerably different to the dimensional model.

3.6. Results and Discussion

This section compares the results obtained from the three proposed models for glucose-insulin-glucagon dynamics during an IVGTT. The models are assessed based on how well they fit the datasets, how the behaviour of glucose and the hormones compared to what is supposed from evidence obtained from previous studies and how the values for the key parameters compare to the acceptable ranges as specified within literature.

The linear model is the simplest of the three, consisting of 4 less quantities than the Glucagon Minimal Model and 3 less than the Linear Glucagon Minimal Model. It is beneficial in that it can be solved analytically and also provided a very good fit to the plasma measurements for glucose. However, the fit to plasma insulin measurements was of a poor quality, and the simulation for plasma glucagon was deemed unrealistic.

The Glucagon Minimal Model was the best model to fit the data for plasma glucose and provided an equally good fit as the Linear Glucagon Minimal Model. Its only downfall is the one extra quantity to be considered than the Linear Glucagon Minimal Model and the results for plasma glucagon; despite showing the correct behaviour the response was of an insufficient magnitude.

The Linear Glucagon Minimal Model provided a good fit to both of the plasma measurements and was able to capture glucagon behaviour. The Glucagon Minimal Model did slightly outperform the model for plasma glucose as the Linear Glucagon Minimal Model did not capture the levels undershooting the basal value quite as well.

The reasonable given range of glucose effectiveness is given as $0.8 - 3.8 \text{ x } 10^{-2}$ (McDonald et al., 2000), which all returned model parameter values are within. It can be seen that the more complex the model is and the more non-linear terms a model has, the lower the value of glucose effectiveness. This may be due to the effects of the terms of glucagon contributing towards hepatic glucose production.

Insulin sensitivity for a healthy individual is typically around $5 \text{ x } 10^{-4}$ (Pacini and Bergman, 1986). The Linear model is not capable of calculating a value for insulin sensitivity; however the other models are within reasonable magnitude of the stated value.

Since there is a limited number of mathematical models for the glucose regulatory system that consider glucagon dynamics at present it is not possible to compare the value returned by the Glucagon Minimal Model. Since it is within reasonable vicinity of insulin sensitivity it is deemed acceptable.

Table 3.8: Comparisons of key parameter values from the three Glucagon Models.

Parameter	Linear Glucagon Model	Glucagon Minimal Model	Linear Glucagon Minimal Model
$S_G = p_1$	0.02717445	0.02059000	0.02808122
S_I	-	1.78999×10^{-5}	7.34737×10^{-4}
S_E	-	6.21902×10^{-4}	-

Comparing the dimensionless simulations of the model it is noticeable that the Linear Glucagon Minimal Model provides a much poorer fit to plasma insulin measurements than the Glucagon Minimal Model. Rescaling the Glucagon Minimal Model for different parameter values resulted in a larger variation of parameters than for the Linear Glucagon Minimal Model. This is likely to be due to the two additional quantities of the Glucagon Minimal Model.

3.7. Summary

This chapter has covered the development of three mathematical models, capable of predicting plasma glucose, insulin and glucagon concentrations following an IVGTT. Each model ranged in its complexity, assuming either linear or non-linear relationships. The Linear Glucagon Minima Model is the most accurate model for predicting blood glucose levels during an IVGTT, and is more simplistic than the Glucagon Minimal Model, which required an additional variable and parameter in the system. Although the simplest, the Linear Glucagon Model is not acceptable as it provides a very poor fit to insulin and an unrealistic prediction for glucagon levels. It is possible that the non-linear terms, i.e. equations for hormone activity, are only required when there are large fluxes in the hormones. This will be further investigated by looking at the system during exercise.

Chapter 4 Exercise and the Glucose Regulatory System

4.1. Introduction

Including the effects of glucagon in a model for glucose regulation has allowed for a more accurate representation of glycaemic control, and admits a model capable of returning to homeostasis after perturbations to the system resulting in either a rise or a fall in plasma glucose concentrations.

Chapter 3 highlighted the role of glucagon after an IVGTT, i.e. after a period where glucose is in what is known as the fed state. The aim of this thesis will now be to model glucose-insulin-glucagon dynamics during periods of low glucose availability.

This chapter examines the major effects had by exercise on the system and reviews the key literature that has attempted to model exercise and the glucose regulatory system. Understanding the major effects of exercise on glucose homeostasis will allow for the identification of both the variables and parameters that will be required in order to develop a mathematical model of the system, which will be covered in Chapter 5.

4.2. Exercise and the Glucose Regulatory System

Individuals are encouraged to regularly take part in exercise for the numerous beneficial effects it has on health, including its ability to positively affect blood pressure(Colberg et al. 2010), improve cardio respiratory fitness, and many cardiovascular risk factors (Valletta et al., 2014). In addition to the cardiovascular system, exercise also promotes metabolic health, and is recognized as a natural, inexpensive tool for controlling diabetes and related complications (Derouich and Boutayeb, 2002), due to its ability to increase insulin sensitivity. For individuals at risk of developing type 2 diabetes, recent studies have shown that the effect of physical activity can lower the risk of the onset of the disease by up to 58% (Colberg et al., 2010) partly due to its ability to counteract insulin resistance (Costa-Junior et al., 2015). Therefore physical exercise is considered as an important factor in the treatment of both type 1 and type 2 diabetes (Goodyear and Kahn, 1998).

4.2.1. Increased Glucose Uptake

During physical activity our bodies expend a greater amount of energy; therefore there is an increase in the demand for glucose to be delivered to the working muscles as they contract. The increase in the rate of glucose uptake will be greater as exercise intensity is amplified (Wasserman and Cherrington, 1991), particularly in scenarios of very high intensity exercise, such as at >80% of VO_2^m, where glucose is the exclusive muscle fuel (Marliss and Vranic, 2002). Exercise is often said to have insulin like effect on blood glucose, due to its mechanisms that work to stimulate glucose transport independently from insulin (Sternlicht et al., 1989). Additionally, there is an increase in the rate of insulin-dependent glucose uptake due to an increase in insulin sensitivity (Dalla man et al., 2009) which causes the body to increase its ability to absorb glucose with insulin, despite the decreased concentration of the hormone within the plasma.

4.2.2. Increased Glucose Production

In attempt to maintain homeostasis, the rate of glucose production in the liver increases simultaneously. The increase in hepatic glucose production is a combination of an increase in the rate of both gluconeogenesis and glycogenolysis, stimulated by the increase in plasma glucagon, increased breakdown of ATP, glycogen (Jeukendrop and Gleeson, 2010), and a decrease in plasma insulin (Wasserman and Cherrington, 1991). Glucose production increases proportionally to the intensity of exercise (Petersen et al, 2004), (Hargreaves and Spriet, 2006). Glycogenolysis typically contributes the most towards hepatic glucose production and is particularly noticed to dominate production early in exercise (Coggan, 1991); however during prolonged periods of activity, available glycogen stores are depleted. As the availability of glycogen declines so does the rate of hepatic glucose production. The amount of available gluconeogenic precursor supplies begins to increase with increasing exercise duration; thus the contribution to glucose production from gluconeogenesis increases, and soon dominates over glycogenolysis (Kjaer, 1998), however is not enough to counterbalance the reduction in glycogenolysis.

4.2.3. Decline in Glycogenolysis

Muscle glycogen is the primary fuel for most types of exercise and is able to provide immediate energy for the muscles.

Glycogenolysis typically contributes the most towards hepatic glucose production and is particularly noticed to dominate production early in exercise (Coggan, 1991) as muscle glycogen is the chief source of energy for contraction (Wasserman and Cherrington, 1991). However during prolonged periods of activity, the availability of glycogen begins to diminish at a rate that is proportional to exercise intensity, thus the rate of glycogenolysis begins to decline (Juekendrup and Gleeson, 2010) until all glycogen stores have been used.

4.2.4. Decreased Plasma Insulin Concentration

During exercise a decrease in the plasma insulin levels is essential to allow fat release for oxidation to occur to enable a sufficient amount of lipids available as a source of energy (MacLaren and Morton, 2012). Healthy patients will experience a decline in plasma insulin concentrations as a result of insulin secretion being inhibited by β-cell α-adrenergic receptor activation (Marliss and Vranic, 2002) and an increase rate of insulin-independent glucose uptake, both of which are part of a glucoregulatory response to avoid hypoglycaemia. A decrease in insulin removal also occurs, although the importance of which during exercise is still unclear, however a decrease in insulin clearance has been linked to overcoming insulin resistance, thus delaying type 2 Diabetes (Costa-Junior et al., 2015).

4.2.5. Increased Plasma Glucagon Concentration

Elevated levels of glucagon during exercise allow for an increase in hepatic glucose production to avoid hypoglycaemia (Lavoie et al., 1997). Research shows that during exercise, signals are sent to the pancreas to increase glucagon secretion. The rate of glucagon secretion in exercise is also affected by plasma glucose concentrations, and decreases with plasma glucose availability (Luyckx et al., 1978).

In longer periods of exercise plasma glucose levels begin to fall as glycogen stores are depleted (Jeukendrup and Gleeson, 2010), which acts as a potent stimulus for plasma glucagon secretion. Typically in prolonged exercise glucagon increases threefold (Galbo et al., 1975) (Vranic et al., 1976), however, studies such as that performed by Ahlborg et al. (1974) demonstrate glucagon to have risen by as much by as five times the resting value.

4.3. Critical Review of Existing Exercise Models

4.3.1. Parameter Modification of The Bergman Minimal Model

Derouich and Boutayeb (2002) adapted the minimal model by introducing parameters that consider the effects of exercise on glucose regulation. The new parameters q_1, q_2 and q_3, mimic the ability of exercise to increase in utilization of both glucose and insulin in addition to the increased sensitivity of the muscles and liver to insulin, such that the equations for plasma glucose and interstitial insulin become:

$$\frac{dG(t)}{dt} = -(1 + q_2) * X(t) * G(t) + (p_1 + q_1) * \big(G_b - G(t)\big), \quad (4.1)$$

$$\frac{dX(t)}{dt} = (p_3 + q_3) * (I(t) - I_b) - p_2 * X(t), \quad (4.2)$$

The steady state analysis of the model shows that the value given for insulin sensitivity is higher with physical activity that the original minimal model which confirms the physiological findings that exercise increases insulin sensitivity (Borghouts and Keizer, 2000), (Holloszy, 2005).

Derouich and Boutayeb (2002) ran simulations for healthy individuals and adjusted the model so that it was able to consider the diabetic state; both type 1 and type 2. Their steady state analysis showed that in the absence of administered insulin both profiles would reach a hyperglycaemic state, where as administration of insulin could easily be perceived as an excess, thus leading to hypoglycaemia.

4.3.2. Introduction of New Variables to The Bergman Minimal Model

Following the work of the Derouich and Boutayeb (2002) was the development of the model by Roy and Parker (2007), whose work also used the minimal model as a foundation to develop their model. This work introduced new variables to the minimal model that account for the physiological changes to the system during exercise.

To quantify the exercise intensity, a term was introduced representing the percentage of the maximum rate of oxygen consumption (PVO_2^{max}), and is described mathematically as:

$$\frac{dPVO_2^{max}}{dt} = -0.8 * PVO_2^{max}(t) + 0.8 * u_3, \tag{4.3}$$

where u_3 is the exercise intensity.

The exercise induced changes of an increase in the rate of glucose production, glucose utilization and decrease in plasma insulin are given by:

$$\frac{dG_{prod}}{dt} = -a_1 * G_{prod}(t) + a_2 * {PVO_2}^{max}(t), \tag{4.4}$$

$$\frac{dG_{up}}{dt} = -a_3 * G_{prod}(t) + a_4 * {PVO_2}^{max}(t), \tag{4.5}$$

$$\frac{dI_e}{dt} = -a_5 * I_e(t) + a_6 * {PVO_2}^{max}(t), \tag{4.6}$$

The model is more sophisticated and physiologically accurate than the parameter extension by Derouich and Boutayeb (2002), as it considers the fact that glucose levels will decline as muscle glycogen is utilized. The decline in glycogenolysis is modelled by creating an energy expenditure threshold and an equation of the integrated exercise intensity, given by:

$$A_{TH} = -1.152 * (u_3)^2 + 87.471 * u_3, \tag{4.7}$$

$$\frac{dA}{dt} = u_3(t), \tag{4.8}$$

The rate of glycogenolysis is dependent on whether or not the value of integrated exercise intensity (4.8) exceeds the energy expenditure threshold (4.7), and is defined as follows:

$$\frac{dG_{gly}}{dt} = \begin{cases} 0, & A(t) < A_{TH} \\ k, & A(t) \geq A_{TH} \\ -\dfrac{G_{gly}(t)}{T_1} & u_3(t) = 0 \end{cases}, \tag{4.8}$$

Roy and Parker's model provides a good fit to the data available for low-moderate exercise; however the model is not able to predict higher levels of exercise.

One explanation could be due to the fact that, the equation for modelling exercise intensity is based on the work of Astrand (1960), thus assuming that oxygen consumption is approximately linearly proportional to energy expenditure. In more recent studies by Barstow and Mole (1991), it was determined that oxygen uptake rose linearly only for lower working rates (38 and 54% of VO_2^{max}), and that the increase was significantly greater for exercising at intensities, (85 and 100% of VO_2^{max}). Therefore this equation may be inadequate for modelling higher working rates.

Another possible reasoning may be due to the fact that the new terms introduced into the model are all linear, which, despite the added benefit of simplicity, they may not be sufficient to accurately represent the complex behaviour that occurs during exercise. Cooper et al. (1989) state that glucose uptake data for exercise at work rates between 40 and 60% of $VO_2{}^{max}$ suggests a non-linear increase between the two, contradicting other research (Katz et al. 1986), (Wahren et al. 1971) that suggests glucose uptake increase in proportion to exercise intensity.

4.3.3. Modelling Exercise with Delay Differential Equations

In 2010, Svitra et al. extended the delay differential equation (DDE) model for insulin and glucose dynamics proposed by Svitra (1989) to take into account the effects of diet and physical activity. Two linear external periodic functions, g(t) and f(t), were introduced and defined as:

$$g_i(t) = g_i(t+24) = \alpha_i \sin\left[\frac{\pi}{T_i}(t - t_{i1})\right], t_{i1} \leq t \leq t_{i2}, \quad (4.9)$$

$$f_j(t) = f_j(t+24) = \gamma_j \sin\left[\frac{\pi}{T_j}\left(t - t_{j1}\right)\right], t_{j1} \leq t \leq t_{j2}, \quad (4.10)$$

where $g(t)$ is the nutritional intake, $i(t)$ is the exercise performed, t_{i1} and t_{j1} are the times the effects begin, t_{i2} and t_{j2} are the times they finish and both T_i and T_j are the duration of the effects of glucose consumption and exercise.

The model is easily implemented and allows for an efficient comparison of a number of different meals and exercise bouts in both healthy and diabetic individuals. Different parameter values are obtained, allowing for an insight into which routine may be the most effective in improving the diabetic state, i.e. increasing the ability to dispose of excess glucose and respond to insulin secretion. Svitra and co-workers performed a thorough mathematical analysis of the model and found a stable equilibrium that could be confirmed with physiological reasoning.

However, there is no detail on how the effect of the meal was quantified; the amount of carbohydrates consumed or the glycaemic index of the meal was not discussed, making it difficult to apply the model in a physical situation. The same issue remains for exercise. It is known that the effects of aerobic exercise on glucose metabolism vary with duration and intensity (Adams, 2013), however there is no explicit term that quantifies the working rate of the exercise being performed.

4.4. Summary

This chapter has given an overview of the fundamental physiological changes that affect the glucose regulatory system during exercise. Key literature was reviewed, identifying the existing approaches and considerations made to modelling exercise.

The chapter then went on to examine the major effects of exercise on the system and to identify the key considerations for model formulations.

With this information, the next chapters will introduce proposed models to simulate blood glucose regulation during exercise. Each model will be fitted to data and analysed mathematically.

Chapter 5 Modelling Exercise

5.1. Introduction

Chapter 4 reviewed the importance of exercise for health, its use in both managing and preventing diabetes and its effects on glucose homeostasis. New terms are added to the models developed in chapter 3 (equations 3.4 – 3.12) to simulate and predict the concentrations of glucose and its regulatory hormones in the plasma during physical activity.

Although chapter 3 determined that a non-linear term was not necessary to produce a model for glucose -glucagon dynamics during an IVGTT, it is expected that this result was due to the fact that there was only a very small increase in plasma glucagon. In this chapter both the Glucagon Minimal Model and Linear Glucagon Minimal Model will be extended for exercise, and will conclude whether a linear term is sufficient for describing glucose-glucagon interactions.

This chapter considers the glucose regulatory system for a healthy individual and does not assume an impaired glucose response. In the presence of T2DM, the effects of exercise on the system would expect to remain the same; however it is likely that the value for insulin sensitivity would still remain lower than for a healthy individual. More research would need to be done to collect datasets from participants with T2DM for the effects to become clear. T1DM is considered in the following chapter.

5.2. Model Formation

Exercise is often described as having an insulin like effect on blood glucose due to its ability to increase the rate of glucose uptake (Goodyear and Kahn, 1998). Therefore the effects of exercise on the system will be modelled in a similar manner to insulin, by introducing a compartment to represent the level of exercise induced activity in the system.

5.2.1. Exercise Variables

5.2.1.1. Exercise Activity

Both exercise intensity and the duration of activity have been identified as the primary factors determining the effects of exercise on blood glucose levels. To quantify exercise intensity, equation (4.3) proposed by Roy and Parker (2007) for the percentage of VO_2^{max} (PVO_2^{max}), will be incorporated into the model and is given by:

$$\frac{dPVO_2^{max}}{dt} = -0.8 * PVO_2^{max}(t) + 0.8 * u_3, \qquad (5.1)$$

where u_3 defines the exercise intensity (Percentage of VO_2^{max}above the basal level) and is equal to zero when time, *t*, is outside of the interval $0 < t < T_{dur}$, where T_{dur} is the duration of exercise. It is worth noting that the equation assumes that the basal level for VO_2^{max} is 8%, which is not entirely accurate, since the value differs based on the fitness of an individual (Dalleck and Dalleck, 2008). The equation by Roy and Parker is also based on the findings of Astrand (1960) who established that oxygen consumption is approximately linearly proportional to energy expenditure. However, in more recent studies by Barstow and Mole (1991) it was determined that oxygen uptake rose linearly only for lower working rates (38 and 54% of VO_2^{max}), and that the increase was significantly greater for exercising at intensities, (85 and 100% of VO_2^{max}). Therefore this equation may be inadequate for modelling higher working rates. This will be reviewed at the end of the chapter.

In this model a new compartment is added (described as cellular exercise activity) to account for the effects of exercise on the glucose regulatory system. The equation proposed is:

$$\frac{dA}{dt} = -p_{11} * A(t) + p_{12} * PVO_2^{max}(t), \qquad (5.2)$$

where α is the rate clearance of exercise induced activity on the glucose regulatory system and β is the increase of activity, proportional to the percentage of an individual's VO_2^{max}. This new variable will be used to account for the exercise induced changes; amplified glucose uptake, decline in plasma insulin and increase in plasma glucagon (Goodwin, 2010), as described by the following variables (5.3-5.8).

5.2.1.2. Increase in Plasma Glucose Uptake

The increased rate of insulin-independent glucose uptake will be modelled by a negative non-linear function of both the plasma glucose concentration and the new variable for exercise activity $A(t)$:

$$-G_{up} = -G(t) * A(t), \tag{5.3}$$

The rate will increase with higher plasma glucose concentrations and with higher levels of exercise intensity.

5.2.1.3. Decrease in Plasma Insulin Concentration

A new term is included into the equation for plasma insulin, (t), to represent the decrease in plasma insulin concentrations during exercise. The term is similar to increased glucose uptake as it will be a negative non-linear function of exercise activity and plasma insulin:

$$-I_{dec} = -A(t) * I(t), \tag{5.4}$$

5.2.1.4. Increase in Plasma Glucagon Concentration

The term for the exercise induced change in the plasma glucagon concentration is similar to plasma insulin, however it will have a positive effect on glucagon production. Therefore, the term is given by:

$$E_{inc} = A(t) * E(t),, \tag{5.5}$$

5.2.1.5. Increase in Hepatic Glucose Production

Hepatic glucose production (HGP), the sum of gluconeogenesis and glycogenolysis, increases during exercise in attempt to balance the increased glucose uptake by muscle to maintain glucose homeostasis (Adams, 2013).

Unlike the model of Roy and Parker, this model will not add a term for increased glucose production, since this model takes into account muscle glycogenolysis and the effects of glucagon to increase (HGP) on the system. In prolonged exercise, it is the rise in plasma glucagon and fall in plasma insulin that is essential to ensure an increase in hepatic glucose production and gluconeogenesis (Lavoie et al. 1997), therefore will not be modelled by an additional term in the model, but indirectly by an increase and decrease in both glucagon and insulin activity, caused by an exercise induced increase in plasma glucagon and decrease in plasma insulin respectively.

Note that since skeletal muscle lacks glucose-6-phosphatase (g6p) and consequently cannot deliver free glucose to the blood via gluconeogenesis (Gluconeogenesis: Endogenous Glucose Synthesis, 2016). Therefore gluconeogenesis is only accounted for by the hepatic terms for glucose regulation.

5.2.1.6. Muscle Glycogen Depletion

Glycogen breakdown and synthesis are reciprocally regulated (Berg et al., 2002), i.e. activation of one simultaneously inhibits the other. This suggests that, as during exercise there is a significant amount of muscle glycogen utilisation (particularly during exercise intensity above 70% of Vo_2^m), (Jensen et al., 2011) muscle glycogen synthesis becomes obsolete . Since this model is only concerned with the system dynamics during exercise, the equation modelling muscle glycogen will focus only on the rate of glycogen degradation stimulated by exercise and not give a detailed consideration to glycogen synthesis. A term will be included such that the long term behaviour corresponds with the physical system, however a simple term will be proposed that is proportional to the amount of glycogen below the. This term will be omitted in the simulations for exercise.

In previous work to model the glycogenolysis pathway (Meinke and Edstrom, 1990), (Todd, 2008), Michaelis-Menten dynamics are assumed for the rate of glycogen depletion. Michaelis-Menten provides a kinetic description of enzyme activity (Berg, 2002) thus is a good basis for describing the reaction of glycogenolysis, which requires different enzymes for the degradation of glycogen (Todd, 2008).

A Michaelis-Menten term for the velocity of a reaction is of the following structure:

$$V = \frac{V_{max} * [S]}{K_m + [S]}, \tag{5.6}$$

where the V_{max} represent the maximum velocity and the Michaelis constant, K_m, indicates the amount of the substrate for the maximum velocity to be reached (Worthington Biochemical Corporation, 2016).
A simple term for Michaelis-Menten kinetics is proposed, proportional to the amount of glycogen in the muscle ($Gly(t)$) and the exercise intensity ($PVO_2^{max}(t)$), therefore the rate will increase as exercise intensity increases and decrease as muscle glycogen availability diminishes.

The equation is given by:

$$\frac{dGly}{dt} = \frac{-\delta * PVO_2^{max}(t) * Gly(t)}{\frac{Gly_b}{2} + Gly(t)} - \mu * (Gly(t) - Gly_b), \quad (5.7)$$

where the maximum velocity is given by δ and the Michaelis constant is fixed to half of the amount of basal glycogen, i.e. the amount of glycogen the body will replenish to in the fed state, $\frac{Gly_b}{2}$.

The rate of glycogenolysis in muscles is most rapid during the first 5 to 10 minutes of exercise (Goldman and Schafer, 2012) and declines as a result of reduced levels of muscle glycogen (Blomstrand and Saltin, 1999). Therefore since the K_m is the substrate concentration that gives the enzyme one-half of its V_{max} (Flynn, 2003), the model assumes that the rate the glycogenolysis will reach half of its initial rate when the amount of glycogen decreases to half of its initial value.

5.2.1.7. Glucose Production via Muscle Glycogenolysis

This model will not include an additional term for liver glycogen, since hepatic glucose production (HGP) glycogen stored in the muscle is considered as a major source of fuel during exercise (Richter et al. 1982), and is stimulated by both muscle contractions and epinephrine. Since this model does not account for the effects of epinephrine at this stage, the term will be proportional to the amount of available glycogen and the level of exercise intensity. The term will not be dependent on the concentration of glucagon since it exerts no direct action on muscle cells (Goodwin, 2010). The increase in the rate of glucose production via muscle glycogenolysis is modelled by:

$$G_{prod} = \rho * \frac{\beta * PVO_2^{max}(t) * Gly(t)}{250 + Gly(t)}, \quad (5.7)$$

where $Gly(t)$ is the amount of muscle glycogen available. The term is proportional to the amount of available muscle glycogen and the amount of energy being expended, therefore the rate will decrease over time as glycogen stores become depleted and increase with the working rate.

5.2.2. The Glucagon Exercise Minimal Model

The relationships and interactions for the first model proposed are shown below in figure 5.1:

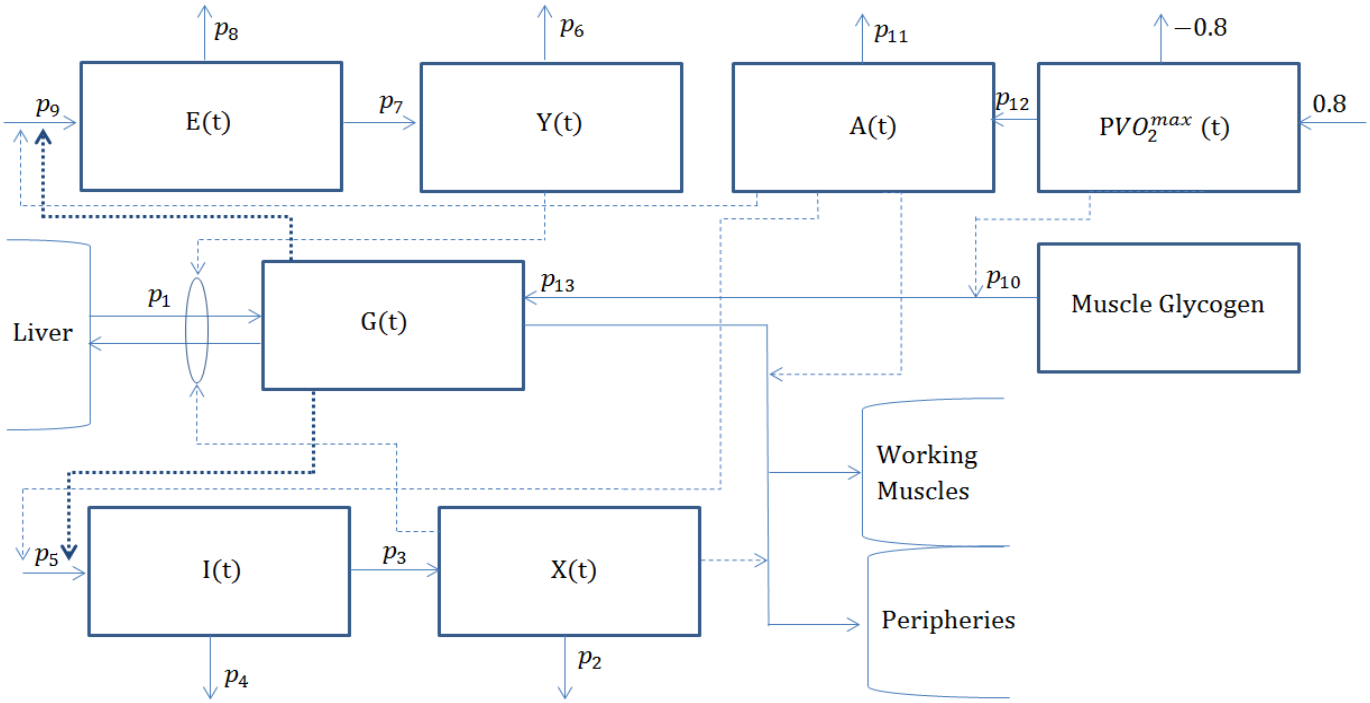


Figure 5.1: Compartment Diagram of Glucose-Insulin-Glucagon dynamics during exercise, assuming a non-linear relationship between glucose and glucagon

Table 5.1: Glucagon Exercise Minimal Model Nomenclature of new parameters.

Parameter	Description	Unit
p_{10}	Michaelis constant of maximum velocity, V_{max}, of exercise induced glycogen breakdown.	min^{-1}
p_{11}	Clearance of exercise induced effects on the glucose regulatory system	min^{-1}
p_{12}	Increase in exercise induced effects on the glucose regulatory system	min^{-1}
p_{13}	Rate of glycogen degradation and conversion to glucose	$(mg/dl)min^{-2}$
p_{14}	Rate of glycogen synthesis	min^{-1}

Table 5.1 describes the new rates for exercise in the model. It can be seen that in this model, exercise increases HGP indirectly, and occurs through the exercise stimulated increase in glucagon activity. This is based on the findings of Lavoie et al. (1997) who concluded that the increase in glucagon during exercise was essential for the increase in HGP and in gluconeogenesis.

The full system is therefore given by:

$$\frac{dG}{dt} = -p_1 * (G(t) - G_b) + G(t) * \big(Y(t) - X(t)\big) + G_{prod} - G_{up}, \tag{5.9}$$

$$\frac{dX}{dt} = -p_2 * X(t) + p_3 * I(t), \tag{5.10}$$

$$\frac{dI}{dt} = -p_4 * (I(t) - I_b) + p_5 * (G(t) - G_b)^+ - I_{dec}, \tag{5.11}$$

$$\frac{dY}{dt} = -p_6 * Y(t) + p_7 * E(t), \tag{5.12}$$

$$\frac{dE}{dt} = -p_8 * (E(t) - E_b) + p_9 * \big(G_b - G(t)\big)^+ + E_{inc}, \tag{5.13}$$

$$\frac{dGly}{dt} = -\frac{p_{10} * PVO_2^{max}(t) * Gly(t)}{250 + Gly(t)} - p_{14} * (Gly(t) - Gly_b), \tag{5.14}$$

$$\frac{dPVO_2^{max}}{dt} = -0.8 * PVO_2^{max}(t) + 0.8 * u_3, \tag{5.15}$$

$$\frac{dA}{dt} = -p_{11} * A(t) + p_{12} * PVO_2^{max}(t), \tag{5.16}$$

Subject to the following initial conditions:

$$G(0) = G_0, \quad X(0) = 0, \quad I(0) = I_0, \quad Y(0) = 0, \quad E(0) = E_0,$$
$$Gly(0) = 500\ (Jensen\ et\ al., 2011), \quad PVO_2^{max}(0) = 0, \quad A(0) = 0$$

5.2.3. The Simplified Glucagon Exercise Minimal Model

In chapter 3, it was proven that a reduced model for glucose-insulin-glucagon dynamics (Chapter 3, Section 3.3.3) was able to predict the behaviour of the system accurately, without an additional compartment for glucagon activity, resulting in two less quantities than the Glucagon Minimal Model.

Therefore a similar approach will be taken for modelling the effects of exercise, removing the equation for glucagon activity, (t), and assuming the effects of excess glucagon on hepatic glucose production to be a linear term. The rest of the model is as given for the Exercise Model 1 (Section 5.1).

The relationship between variables is as shown in figure 5.2:

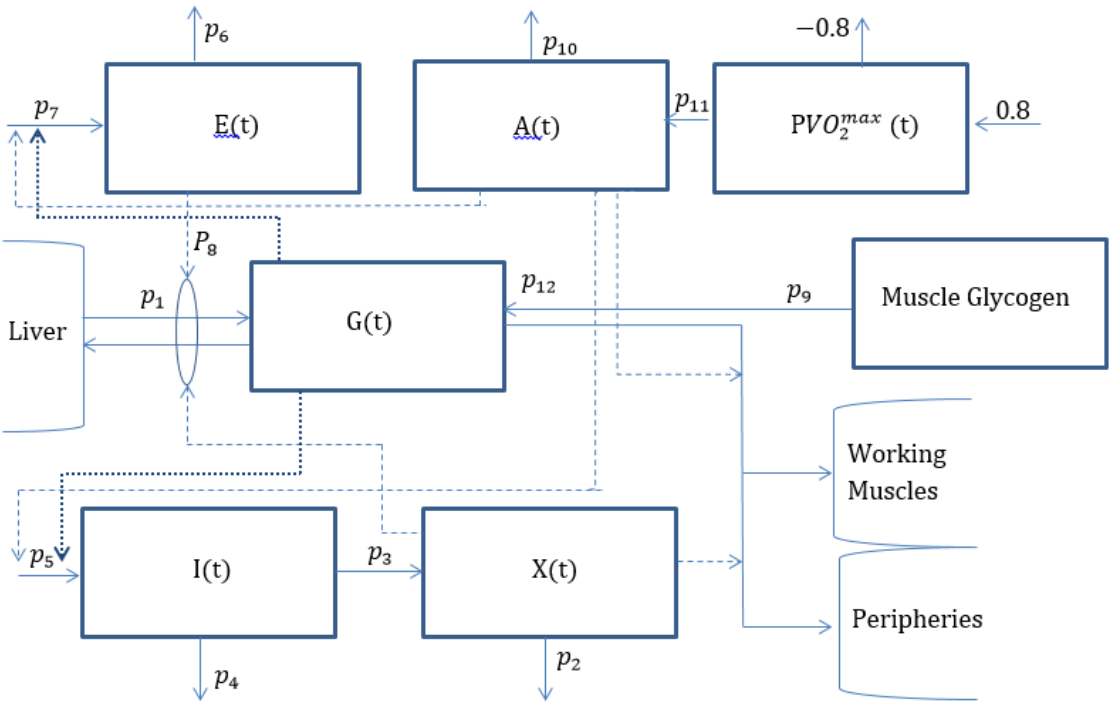


Figure 5.2: Compartment Diagram of Glucose-Insulin-Glucagon dynamics during exercise, assuming a linear relationship between glucose and glucagon

Table 5.2 summarises the new rates for exercise in the model.

Table 5.2: Linear Glucagon Exercise Minimal Model Nomenclature of new parameters.

Parameter	Description	Unit
p_9	Michaelis constant of maximum velocity, V_{max}, of exercise induced glycogen breakdown.	min^{-1}
p_{10}	Decrease of exercise induced effects on the glucose regulatory system	min^{-1}
p_{11}	Increase in exercise induced effects on the glucose regulatory system	min^{-1}
p_{12}	Rate of glycogen degradation and conversion to glucose	$(mg/dl)min^{-2}$
p_{13}	Rate of glycogen synthesis	min^{-1}

The full system is given by:

$$\frac{dG}{dt} = -p_1 * (G(t) - G_b) - G(t) * X(t) + G_{prod} - G_{up} + P_8 * (E(t) - E_b)^+, \quad (5.17)$$

$$\frac{dX}{dt} = -p_2 * X(t) + p_3 * I(t), \quad (5.18)$$

$$\frac{dI}{dt} = -p_4 * (I(t) - I_b) + p_5 * (G(t) - G_b)^+ - I_{dec}, \quad (5.19)$$

$$\frac{dE}{dt} = -p_6 * (E(t) - I_b) + p_7 * \left(G_b - G(t)\right)^+ + E_{inc}, \quad (5.20)$$

$$\frac{dGly}{dt} = -\frac{p_9 * PVO_2^{max}(t) * Gly(t)}{\frac{Gly_b}{2} + Gly(t)} - p_{13} * (Gly(t) - Gly_b), \quad (5.21)$$

$$\frac{dPVO_2^{max}}{dt} = -0.8 * PVO_2^{max}(t) + 0.8 * u_3, \quad (5.22)$$

$$\frac{dA}{dt} = -p_{10} * A(t) + p_{11} * PVO_2^{max}(t), \quad (5.23)$$

Subject to the following initial conditions:

$G(0) = G_0,\ \ X(0) = 0,\ \ I(0) = I_0,\ \ E(0) = E_0, Gly(0) = 500$ (*Jensen et al.*, 2011),

$PVO_2^{max}(0) = 0,\ \ A(0) = 0.$

5.3. Model Analyses

The system of equations (5.9-5.23) is subject to initials condition that are all greater than or equal to zero. The model considers concentrations within the plasma, energy stores of glycogen, the working rate of exercise, the activity of exercise to affect glucose homeostasis and the activity of the hormones to stimulate glucose production and disappearance. Since these are all biological reflections, all variables must be positive. Based on the approach of Magombedze et al. (2009) the following theorem is given, guaranteeing a well posed system

Positive-Definitive Theorem

The system of equations (5.9-5.16) is positively invariant, ensuring a positive solution existing for all time $0 < t < \infty$. This can be proved as follows:

The components of the system $G, X, I, Y, E, Gly, PVO_2^{max}$ and A under the initial conditions are positive for all $t > 0$. This is proved by assuming the logical negation, i.e. proof by contradiction, therefore we assume that there exists a time such that:
$G(t_i) = 0, G'(t_i) \leq 0$ and $G(t) > 0, X(t) > 0, I(t) > 0, Y(t) > 0, E(t) > 0, Gly(t) > 0,$
$(t) > 0$ and $PVO^{ma}_2(t) > 0$, for $0 < t < \quad t_i$,

or there exists a time t_j such that:
$PVO_2^{max}(t_j) = 0, PVO_2^{max\prime}(t_j) \leq 0$ and $PVO_2^{max}(t) > 0, G(t) > 0, I(t) > 0, Y(t) > 0, E(t) > 0, Gly(t) > 0, A(t) > 0$ and $X(t) > 0$, for $0 < t < t_j$.
By substituting in the terms for G_{prod} and $-G_{up}$ equation (5.9) becomes:

$$\frac{dG(t_i)}{dt} = p_1 * G_b - G(t_i) * (X(t_i) - Y(t_i) + A(t_i) + p_1) + p_{13} * \frac{(p_{10} * Gly(t_i) * PVO_2^{max}(t_i))}{250 + Gly(t_i)}, \quad (5.24)$$

which reduces to

$$p_1 * G_b + p_{13} * \frac{(p_{10} * Gly(t_i) * PVO_2^{max}(t_i))}{250 + Gly(t_i)} > 0, \quad (5.25)$$

At time t_j equation (5.1) states that

$$\frac{dPVO_2^{max}(t_j)}{dt} = -0.8 * PVO_2^{max}(t_j) + 0.8 * u_3, \tag{5.26}$$

which reduces to

$$0.8 * u_3 > 0, \tag{5.27}$$

which are both contradictions. Similarly this holds for the remaining equations, which never reach less than zero. Thus it can be concluded that the system of equations (5.17-5.23) remains positive for all $t > 0$.

Note that this theorem holds for both models presented in this chapter.

5.3.1 The Glucagon Exercise Minimal Model

This section will consist of a non-dimensional analysis of the equations (5.9-5.16). The theory and implications of rescaling and non-dimensionalizing a model is described in section 3. 4.3. The first step when non-dimensionalizing a model is to identify the dimensions of the variables and parameters in the model (table 5.3)

Table 5.3: Dimensions of variables in Glucagon Exercise Minimal Model.

Symbol	**Description**	**Unit**	**Dimension**		
			M	**L**	**T**
G(t)	*Plasma Glucose concentration at time t*	mg/dl	1	-3	0
I(t)	*Plasma Insulin concentration at time t*	$\mu U/ml$	1	-3	0
X(t)	*Interstitial Insulin activity at time t*	min^{-1}	0	0	-1
Y(t)	*Glucagon activity at time t*	min^{-1}	0	0	-1
E(t)	*Plasma Glucagon concentration at time t*	pg/ml	1	-3	0
Gly(t)	*Amount of muscle glycogen at time t*	G	1	0	0
$PVO_2^{max}(t)$	*Percentage of* VO_2^{max} at the time	%	0	0	0
A(t)	*Exercise activity at time t*	min^{-1}	0	0	-1

Table 5.4: Dimensions of parameters in The Glucagon Exercise Minimal Model.

Symbol	Description	Unit	Dimension		
			M	L	T
p_1	*Glucose Effectiveness*	min^{-1}	0	0	-1
p_2	*Rate of tissue glucose uptake ability*	min^{-1}	0	0	-1
p_3	*Rate of excess plasma insulin stimulated insulin activity*	$(\mu\, U/ml)^{-1}min^{-2}$	-1	3	-2
p_4	*Insulin disappearance*	min^{-1}	0	0	-1
p_5	*Rate of second phase insulin secretion (glucose dependent)*	$(\mu U/ml)min^{-1}$	0	0	-1
p_6	*Rate of cellular glucose production ability*	min^{-1}	0	0	-1
p_7	*Rate of excess plasma glucagon stimulated insulin activity*	$(pg\ ml)^{-1}min^{-2}$	-1	3	-2
p_8	*Glucagon clearance*	min^{-1}	0	0	-1
p_9	*Glucose dependent Glucagon secretion*	$(pg\ ml)min^{-1}$	0	0	-1
p_{10}	*Maximum velocity for glycogen degradation during exercise*	$(g)\ min^{-1}$	1	0	-1
p_{11}	*Rate of clearance of cellular exercise stimulated activity*	min^{-1}	0	0	-1
p_{12}	*Rate of increase of* PVO_2^{max} *above basal level stimulated exercise*	min^{-2}	0	0	-2
p_{13}	*Rate of glucose production as a result of muscle glycogenolysis*	$(mg/dl)\ min^{-1}$	1	-3	-1
p_{14}	*Rate of glycogen synthesis*	min^{-1}	0	0	-1
G_b	*Baseline plasma glucose concentration*	mg/dl	1	-3	0
I_b	*Baseline plasma insulin concentration*	$\mu U/ml$	1	-3	0
E_b	*Baseline plasma glucagon concentration*	pg/ml	1	-3	0
Gly_b	*Amount of baseline muscle glycogen*	g	1	0	0

The next step is to convert the original variables to the dimensionless form. Note that all the barred variable and parameters are unitless. Let

$$G = G_b * \tilde{G}, \qquad I = I_b * \tilde{I}, \qquad E = E_b * \tilde{E}, \qquad X = \frac{\tilde{X}}{\tau}, \qquad Y = \frac{\tilde{Y}}{\tau},$$

$$Gly = Gly_b * Gl\tilde{y}, \;\; PVO_2^{max} = \frac{\widetilde{PVO_2^{max}}}{\tau} \;\; A = \frac{\tilde{A}}{\tau} \;\; \text{and} \;\; t = \tau * T.$$

Note that

$\frac{d}{dt} = \frac{d}{dT} * \frac{dT}{dt} = \frac{1}{\tau} * \frac{d}{dT}$

The system can now be rewritten in dimensionless form as follows:

$$\frac{d\tilde{G}}{dT} = -p_1 * \tau * \left(\tilde{G} - 1\right) + \tilde{G} * \left(\tilde{Y} - \tilde{X} - \tilde{A}\right) + \frac{p_{13} * p_{10} * Gl\tilde{y} * \widetilde{PVO_2^{max}}}{G_b * \left(\frac{1}{2} + Gl\tilde{y}\right)}, \tag{5.28}$$

$$\frac{d\tilde{X}}{dT} = -p_2 * \tilde{X} * \tau + p_3 * I_b * \tau^2 * \tilde{I}, \tag{5.29}$$

$$\frac{d\tilde{I}}{dT} = -p_4 * \tau * (\tilde{I} - 1) + \frac{p_5 * G_b * \tau}{I_b} * \left(\tilde{G} - 1\right)^+ - \tilde{I} * \tilde{A}, \tag{5.30}$$

$$\frac{d\tilde{Y}}{dT} = -p_6 * \tilde{Y} * \tau + p_7 * E_b * \tau^2 * \tilde{E}, \tag{5.31}$$

$$\frac{d\tilde{E}}{dT} = -p_8 * \tau * \left(\tilde{E} - 1\right) + \frac{p_9 * G_b * \tau}{E_b} * \left(1 - \tilde{G}\right)^+ + \tilde{A} * \tilde{E}, \tag{5.32}$$

$$\frac{dGl\tilde{y}}{dT} = -\frac{p_{10} * Gl\tilde{y} * \widetilde{PVO_2^{max}}}{Gly_b * \left(\frac{1}{2} + Gl\tilde{y}\right)} - p_{14} * \tau * (Gl\tilde{y} - 1), \tag{5.33}$$

$$\frac{d\widetilde{PVO_2^{max}}}{dT} = -0.8 * \widetilde{PVO_2^{max}} * \tau + 0.8 * \tau^2 * u_3, \tag{5.34}$$

$$\frac{d\tilde{A}}{dT} = -p_{11} * \tilde{A} * \tau + p_{12} * \tau * \widetilde{PVO_2^{max}}, \tag{5.35}$$

The natural time scales of the minimal were identified as $\frac{1}{p_1}$, the time scale of insulin dependent glucose disappearance, and $1/p_4$, the time scale of insulin disappearance (Nittala et al., 2006). The natural time scales of this model also include glucagon disappearance.

Choosing to rescale the system by $\tau = \frac{1}{p_1}$ gives

$$\frac{d\tilde{G}}{dT} = 1 + \tilde{G} * \left(\tilde{Y} - \tilde{X} - \tilde{A} - 1\right) + \frac{\widetilde{p_{13}} * Gl\tilde{y} * \widetilde{PVO_2^{max}}}{(1/2 + Gl\tilde{y})} \tag{5.36}$$

$$\frac{d\tilde{X}}{dT} = -\widetilde{p_2} * \tilde{X} + \widetilde{p_3} * \tilde{I}, \tag{5.37}$$

$$\frac{d\tilde{I}}{dT} = -\widetilde{p_4} * (\tilde{I} - 1) + \widetilde{p_5} * \left(\tilde{G} - 1\right)^+ - \tilde{I} * \tilde{A}, \tag{5.38}$$

$$\frac{d\tilde{Y}}{dT} = -\widetilde{p_6} * \tilde{Y} + \widetilde{p_7} * \tilde{E}, \tag{5.39}$$

$$\frac{d\tilde{E}}{dT} = -\widetilde{p_8} * \left(\tilde{E} - 1\right) + \widetilde{p_9} * \left(1 - \tilde{G}\right)^+ + \tilde{A} * \tilde{E}, \tag{5.40}$$

$$\frac{dGl\tilde{y}}{dT} = -\frac{\widetilde{p_{10}} * Gl\tilde{y} * \widetilde{PVO_2^{max}}}{\left(\frac{1}{2} + Gl\tilde{y}\right)} - \widetilde{p_{14}} * (Gl\tilde{y} - 1), \tag{5.41}$$

$$\frac{d\widetilde{PVO_2^{max}}}{dT} = -\frac{0.8 * \widetilde{PVO_2^{max}}}{p_1} + \frac{0.8 * u_3}{p_1^2}, \tag{5.42}$$

$$\frac{d\tilde{A}}{dT} = -\widetilde{p_{11}} * \tilde{A} + \widetilde{p_{12}} * \widetilde{PVO_2^{max}}, \tag{5.43}$$

Where

$\widetilde{p_2} = \frac{p_2}{p_1}, \widetilde{p_3} =, \widetilde{p_4} = \frac{p_4}{p_1} \widetilde{p_5} = \frac{p_5 * G_b}{p_1 * I_b}$, $\widetilde{p_6} = \frac{p_6}{p_1}, \widetilde{p_7} = \frac{p_7 * E_b}{p_1^2}, \widetilde{p_8} = \frac{p_8}{p_1}, \widetilde{p_9} = \frac{p_9 * G_b}{p_1 * E_b}$,

$\widetilde{p_{10}} = \frac{p_{10}}{Gly_b}, \widetilde{p_{11}} = \frac{p_{11}}{p_1}, \widetilde{p_{12}} = \frac{p_{12}}{p_1}, \widetilde{p_{13}} = \frac{p_{13.}}{G_b} * \frac{p_{10}}{Gly_b}$ *and* $\widetilde{p_{14}} = \frac{p_{14}}{p_1}$.

The initial conditions then become

$$\tilde{G}(0) = \frac{G_b}{G_b} = 1, \tilde{X}(0) = 0, \tilde{I}(0) = \frac{I_b}{I_b} = 1, \tilde{Y}(0) = 0, \tilde{E}(0) = \frac{E_b}{E_b} = 1,$$

$$Gl\tilde{y}(0) = \frac{Gly_b}{Gly_b} = 1, \widetilde{PVO_2^{max}}(0) = 0 \text{ and } \tilde{A}(0) = 0.$$

The critical points of a system refer to the long term behaviour of the system, in which it is assumed that the individual will have stopped exercising, either by choice or exhaustion, i.e. $u_3 = 0$.

By setting the equations (5.27-5.34) equal to zero the system can be rewritten to give the following:

$$\tilde{G} = \frac{1}{\tilde{X} - \tilde{Y}}, \tag{5.44}$$

$$\tilde{X} = \frac{\widetilde{p_3}}{\widetilde{p_2}} * \tilde{I}, \tag{5.45}$$

$$\tilde{I} = \frac{\widetilde{p_4} + \widetilde{p_5} * \left(\tilde{G} - 1\right)^+}{\widetilde{p_4}}, \tag{5.46}$$

$$\tilde{Y} = \frac{\widetilde{p_7}}{\widetilde{p_6}} * \tilde{E}, \tag{5.47}$$

$$\tilde{E} = \frac{\widetilde{p_8} + \widetilde{p_9} * \left(1 - \tilde{G}\right)^+}{\widetilde{p_8}}, \tag{5.48}$$

$$Gl\tilde{y} = 1, \tag{5.49}$$

$$PV\widetilde{O_2^{max}} = 0, \tag{5.50}$$

$$\tilde{A} = 0, \tag{5.51}$$

The system reduces to give the critical point of the non-dimensionalized system as

$$\left(\frac{1}{\frac{\widetilde{\widetilde{p_2}}}{\widetilde{p_2}} - \frac{\widetilde{\widetilde{p_7}}}{\widetilde{p_6}}}, \frac{\widetilde{p_2}}{\widetilde{p_2}}, 1, \frac{\widetilde{p_7}}{\widetilde{p_6}}, 1,1,0,0\right)$$

The point is the only existing critical point of the system, and refers to the basal state, which is the post-absorptive state the individual was in prior to the exercise protocol. The critical point of the dimensional system is

$$\left(\frac{G_b}{\frac{\widetilde{\widetilde{p_2}}}{\widetilde{p_2}} - \frac{\widetilde{\widetilde{p_7}}}{\widetilde{p_6}}}, \frac{\widetilde{p_3}}{\widetilde{p_2}} I_b, I_b, \frac{\widetilde{p_6}}{p_{\tilde{7}}} E_b, E_b, Gly_b, 0,0\right)$$

The Jacobian matrix evaluated at the critical point is given as:

$$J_3 = \begin{bmatrix} -1 - \frac{\widetilde{p_2}}{\widetilde{p_2}} + \frac{\widetilde{p_7}}{\widetilde{p_6}} & -1 & 0 & 1 & 0 & 0 & 2 * \frac{\widetilde{p_{13}}}{3} & -1 \\ 0 & -\widetilde{p_2} & \widetilde{p_3} & 0 & 0 & 0 & 0 & 0 \\ \widetilde{p_5} & 0 & -\widetilde{p_4} & 0 & 0 & 0 & 0 & -1 \\ 0 & 0 & 0 & -\widetilde{p_6} & \widetilde{p_7} & 0 & 0 & 0 \\ -\widetilde{p_9} & 0 & 0 & 0 & -\widetilde{p_8} & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & -\widetilde{p_{14}} & -2 * \frac{\widetilde{p_{10}}}{3} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\frac{0.8}{p_1} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \widetilde{p_{12}} & -\widetilde{p_{11}} \end{bmatrix} \quad (5.52)$$

The characteristic polynomial was determined in Mathematica (See appendix) as:

$$\begin{aligned} (det - J_3\ \lambda) = \left(\frac{0.8}{p_1} + \lambda\right)(-\widetilde{p_{11}} - \lambda)(\widetilde{p_{14}} + \lambda)\left(-\widetilde{p_9}\ (\widetilde{p_2}\ \widetilde{p_4}\ \widetilde{p_7} + (\widetilde{p_2} + \widetilde{p_4})\widetilde{p_7}\ \lambda - \widetilde{p_7}\ \lambda^2\right) \\ + (\widetilde{p_6} + \lambda)(\widetilde{p_8} + \lambda)(-\widetilde{p_2}\ \widetilde{p_4} - \widetilde{p_3}\ \widetilde{p_5} - \widetilde{p_2}\ \lambda - \widetilde{p_4}\ \lambda - \widetilde{p_2}\ \widetilde{p_4}\ \lambda - \lambda^2 - \widetilde{p_2}\ \lambda^2 \\ - \widetilde{p_4}\ \lambda^2 - \lambda^3)\Big) = 0 \end{aligned} \quad (5.53)$$

The roots of the system were determined using the Roots function in Mathematica and will not be written explicitly in this thesis due to the complexity and length of the values, however it is noted that these values are all negative, thus the stability criteria for a linearized model holds.

5.3.2 The Simplified Glucagon Exercise Minimal Model

This section will involve a mathematical analysis of the second model proposed for exercise. It will follow a similar structure to the analysis of the Glucagon Exercise Minimal Model in section 5.3.1.

The variables in the model are listed in table 5.4 along with their units and dimensions in terms of mass, length and time.

Table 5.5: Dimensions of variables in the Simplified Glucagon Exercise Minimal Model.

Symbol	Description	Unit	Dimension		
			M	**L**	**T**
G(t)	*Plasma Glucose concentration at time t*	mg/dl	1	-3	0
I(t)	*Plasma Insulin concentration at time t*	$\mu U/ml$	1	-3	0
X(t)	*Interstitial Insulin activity at time t*	min^{-1}	0	0	-1
Y(t)	*Glucagon activity at time t*	min^{-1}	0	0	-1
E(t)	*Plasma Glucagon concentration at time t*	pg/ml	1	-3	0
Gly(t)	*Amount of muscle glycogen at time t*	g	1	0	0
PVO_2^{max}	*Percentage of* VO_2^{max} *at time ti*	%	0	0	0
A(t)	*Exercise activity at time t*	min^{-1}	0	0	-1

Table 5.6: Dimensions of parameters in Simplified Glucagon Exercise Minimal Model

Symbol	Description	Unit	Dimension		
			M	**L**	**T**
p_1	*Glucose Effectiveness*	min^{-1}	0	0	-1
p_2	*Rate of tissue glucose uptake ability*	min^{-1}	0	0	-1
p_3	*Rate of excess plasma insulin stimulated insulin activity*	$(\mu\, U/ml)^{-1}min^{-2}$	-1	3	-2
p_4	*Insulin disappearance*	min^{-1}	0	0	-1
p_5	*Rate of second phase insulin secretion (glucose dependent)*	$(\mu U/ml)min^{-1}$	0	0	-1
p_6	*Glucagon clearance*	min^{-1}	0	0	-1
p_7	*Glucose dependent glucagon secretion*	$(pg\ ml)min^{-1}$	0	0	-1
P_8	*Glucagon stimulated glucose production*	$(mg/dl)min^{-1}$	0	0	-1
p_9	Michaelis constant of maximum velocity, V_{max}, of exercise induced glycogen breakdown.	$(g)\ min^{-1}$	1	0	-1
p_{10}	Decrease of exercise induced effects on the glucose regulatory system	min^{-1}	0	0	-1
p_{11}	Increase in exercise induced effects on the glucose regulatory system	min^{-2}	0	0	-2
p_{12}	Rate of glycogen degradation and conversion to glucose	$(mg/dl)\ min^{-1}$	1	-3	-1
p_{13}	Rate of glycogen synthesis	min^{-1}	0	0	-1
G_b	*Baseline plasma glucose concentration*	mg/dl	1	-3	0
I_b	*Baseline plasma insulin concentration*	$\mu U/ml$	1	-3	0
E_b	*Baseline plasma glucagon concentration*	pg/ml	1	-3	0
Gly_b	*Amount of baseline muscle glycogen*	G	1	0	0

As shown for the Glucagon Exercise Minimal Model, the original variables are converted to give the dimensionless form. Note that all the barred variables and parameters are unitless.

Let

$$G = G_b * \tilde{G}, \qquad I = I_b * \tilde{I}, \qquad E = E_b * \tilde{E}, \qquad X = \frac{\tilde{X}}{\tau},$$

$$Gly = Gly_b * Gl\tilde{y}, \;\; PVO_2^{max} = \frac{\widetilde{PVO_2^{max}}}{\tau} \;\; A = \frac{\tilde{A}}{\tau} \;\; \text{and} \;\; t = \tau * T.$$

Note that

$$\frac{d}{dt} = \frac{d}{dT} * \frac{dT}{dt} = \frac{1}{\tau} * \frac{d}{dT}$$

The system can now be rewritten in the dimensionless form as follows:

$$\frac{d\tilde{G}}{dT} = -p_1 * \tau * \left(\tilde{G} - 1\right) - \tilde{G} * \left(\tilde{X} + \tilde{A}\right) + \frac{p_{12} * p_9 * \tau * Gl\tilde{y} * \widetilde{PVO_2^{max}}}{G_b * \left(\frac{1}{2} + Gl\tilde{y}\right)} \tag{5.54}$$

$$+ \frac{p_8 * E_b * \tau}{G_b} * \left(\tilde{E} - 1\right), \qquad ,$$

$$\frac{d\tilde{X}}{dT} = -p_2 * \tilde{X} * \tau + p_3 * I_b * \tau^2 * \tilde{I}, \tag{5.54}$$

$$\frac{d\tilde{I}}{dT} = -p_4 * \tau * (\tilde{I} - 1) + \frac{p_5 * G_b * \tau}{I_b} * \left(\tilde{G} - 1\right) - \tilde{I} * \tilde{A}, \tag{5.55}$$

$$\frac{d\tilde{E}}{dT} = -p_6 * \tau * \left(\tilde{E} - 1\right) + \frac{p_7 * G_b * \tau}{E_b} * \left(1 - \tilde{G}\right) + \tilde{A} * \tilde{E}, \tag{5.56}$$

$$\frac{dGl\tilde{y}}{dT} = -\frac{p_9 * Gl\tilde{y} * \widetilde{PVO_2^{max}}}{Gly_b * \left(\frac{1}{2} + Gl\tilde{y}\right)} - p_{13} * \tau * (Gl\tilde{y} - 1) * \left(1 - \frac{u_3}{u_3}\right), \tag{5.57}$$

$$\frac{d\widetilde{PVO_2^{max}}}{dT} = -0.8 * \widetilde{PVO_2^{max}} * \tau + 0.8 * \tau^2 * u_3, \tag{5.58}$$

$$\frac{d\tilde{A}}{dT} = -p_{10} * \tilde{A} * \tau + p_{11} * \tau * \widetilde{PVO_2^{max}}, \tag{5.59}$$

As discussed in section 5.3.1, there are three natural timescales in the system.

Choosing to rescale for glucagon clearance, let $\tau = \frac{1}{p_6}$:

$$\frac{d\tilde{G}}{dT} = -\widetilde{p_1} * \left(\tilde{G} - 1\right) - \tilde{G} * \left(\tilde{X} + \tilde{A}\right) + \frac{\widetilde{p_{12}} * \widetilde{p_{10}} * Gl\tilde{y} * \widetilde{PVO_2^{max}}}{\left(\frac{1}{2} + Gl\tilde{y}\right)} + \widetilde{P_8} * \left(\tilde{E} - 1\right), \tag{5.60}$$

$$\frac{d\tilde{X}}{dT} = -\widetilde{p_2} * \tilde{X} + \widetilde{p_3} * \tilde{I}, \tag{5.61}$$

$$\frac{d\tilde{I}}{dT} = -\widetilde{p_4} * (\tilde{I} - 1) + \widetilde{p_5} * \left(\tilde{G} - 1\right) - \tilde{I} * \tilde{A}, \tag{5.62}$$

$$\frac{d\tilde{E}}{dT} = -\left(\tilde{E} - 1\right) + \widetilde{p_7} * \left(1 - \tilde{G}\right) + \tilde{A} * \tilde{E}, \tag{5.63}$$

$$\frac{dGl\tilde{y}}{dT} = -\frac{\widetilde{p_9} * Gl\tilde{y} * \widetilde{PVO_2^{max}}}{\left(\frac{1}{2} + Gl\tilde{y}\right)} - \widetilde{p_{13}} * (Gl\tilde{y} - 1), \tag{5.64}$$

$$\frac{d\widetilde{PVO_2^{max}}}{dT} = -0.8 * \frac{\widetilde{PVO_2^{max}}}{p_6} + \frac{0.8}{p_6^2} * u_3, \tag{5.65}$$

$$\frac{d\tilde{A}}{dT} = -\widetilde{p_{10}} * \tilde{A} + \widetilde{p_{11}} * \widetilde{PVO_2^{max}}, \tag{5.66}$$

Where

$$\widetilde{p_1} = \frac{p_1}{p_6}, \widetilde{p_2} = \frac{p_2}{p_6}, \widetilde{p_3} = p_3 * \frac{I_b}{p_6^2}, \widetilde{p_4} = \frac{p_4}{p_6}, \widetilde{p_5} = \frac{p_5 * G_b}{I_b * p_6}, \widetilde{p_7} = \frac{p_7 * G_b}{E_b * p_6}, \widetilde{p_8} = \frac{\widetilde{p_8 * E_b}}{G_b * p_6},$$

$$\widetilde{p_9} = \frac{p_9}{Gly_b}, \widetilde{p_{10}} = \frac{p_{10}}{p_6}, \widetilde{p_{11}} = \frac{p_{11}}{p_6}, \widetilde{p_{12}} = \frac{p_{12}}{G_b} \text{ and } \widetilde{p_{13}} = \frac{p_{13}}{p_6}.$$

where

$$\widetilde{p_1} = \frac{p_1}{p_6}, \widetilde{p_2} = \frac{p_2}{p_6}, \widetilde{p_3} = p_3 * \frac{I_b}{p_6^2}, \widetilde{p_4} = \frac{p_4}{p_6}, \widetilde{p_5} = \frac{p_5 * G_b}{I_b * p_6}, \widetilde{p_7} = \frac{p_7 * G_b}{E_b * p_6}, \widetilde{p_8} = \frac{\widetilde{p_8 * E_b}}{G_b * p_6},$$

$$\widetilde{p_9} = \frac{p_9}{Gly_b}, \widetilde{p_{10}} = \frac{p_{10}}{p_6}, \widetilde{p_{11}} = \frac{p_{11}}{p_6}, \widetilde{p_{12}} = \frac{p_{12}}{G_b} \text{ and } \widetilde{p_{13}} = \frac{p_{13}}{p_6}$$

The initial conditions then become

$\tilde{G}(0) = 1, \tilde{X}(0) = 0, \tilde{I}(0) = 1, \tilde{E}(0) = 1, Gl\tilde{y}(0) = 1, \widetilde{PVO_2^{max}}(0) = 0$ and $\tilde{A}(0) = 0$.

The critical points of a system refer to the long term behaviour of the system, in which it is assumed that the individual will have stopped exercising.

By setting the system of equations (5.61-5.67) equal to zero and rearranging gives the non-dimensional system as follows:

$$\tilde{G} = \frac{\widetilde{p_1} * \widetilde{p_2}}{\widetilde{p_3}}, \tag{5.68}$$

$$\tilde{X} = \frac{\widetilde{p_3}}{\widetilde{p_2}}, \tag{5.69}$$

$$\tilde{I} = \widetilde{p_4} + \widetilde{p_5} * \frac{\left(\tilde{G} - 1\right)^+}{\widetilde{p_4}}, \tag{5.70}$$

$$\tilde{E} = 1 + \widetilde{p_7} * \left(1 - \tilde{G}\right)^+, \tag{5.71}$$

$$\widetilde{Gly} = 1, \tag{5.72}$$

$$\widetilde{PVO_2^{max}} = 0, \tag{5.73}$$

$$\tilde{A} = 0, \tag{5.74}$$

Therefore it can be seen that, over time, both insulin and glucagon ensure glucose returns to the basal state, resulting in the critical point of the system to be at $(1, \frac{\widetilde{p_3}}{\widetilde{p_2}}, 1, 1, 1, 0, 0)$. The point is the only existing critical point of the system, and refers to the same state of the system at the beginning of the exercise protocol.

The Jacobian matrix evaluated at the critical point is given as:

$$J_4 = \begin{bmatrix} -\widetilde{p_1} - \frac{\widetilde{p_3}}{\widetilde{p_2}} & -1 & 0 & \widetilde{P_8} & 0 & 2 * \widetilde{p_{10}} * \frac{\widetilde{p_{12}}}{3} & -1 \\ 0 & -\widetilde{p_2} & \widetilde{p_3} & 0 & 0 & 0 & 0 \\ \widetilde{p_5} & 0 & \widetilde{p_4} & 0 & 0 & 0 & -1 \\ -\widetilde{p_7} & 0 & 0 & -1 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & -\widetilde{p_{13}} & -2 * \frac{\widetilde{p_{10}}}{3} & 0 \\ 0 & 0 & 0 & 0 & 0 & -\frac{0.8}{p_6} & 0 \\ 0 & 0 & 0 & 0 & 0 & \widetilde{p_{11}} & -\widetilde{p_{10}} \end{bmatrix} \tag{5.75}$$

Therefore the characteristic equation is given by:

The characteristic equation and roots were calculated in Mathematica,. The roots are all negative, thus the system is stable.

5.4. Model Simulations

Both models are implemented in MATLAB to simulate the components within the glucose regulatory system for various exercise intensities and durations. The model parameters u_3 and T_{dur} are fixed to adjust the simulations for various exercise intensities and durations respectively, replicating the protocols to the data obtained from the various studies used to validate the models.

The datasets used to validate the models are obtained from Ahlborg et al. (1974), Wolfe et al. (1984), Ahlborg and Felig (1982) and Campbell et al. (2014). Each dataset consists of plasma measurements of glucose, insulin and glucagon, all taken at regular intervals. There are approximately 5 measurements of each concentration for each data set. Although this is a sufficient amount of data to be able to understand the behaviour of glucose and the hormones during exercise, given the scale of the models it is an insufficient number of points to return an individual set of parameters, and results in large confidence intervals for the individual parameters (see appendix).

It is expected that the amount of physiological exercise induced effects ought to increase with increasing energy expenditure, which is reflected by the level of exercise activity, (t). The total amount of energy expenditure is a function of the duration of exercise, the intensity, the weight of the individual and the activity (Moore, 2011). This presents some difficulty in determining the value of energy expenditure for each of the simulations, given that the data used has not been obtained from the same individual, and not all of the studies consisted of the same activity. It can be seen from Moore (2011) that running and cycling have very similar energy expenditure values, therefore it will be assumed that the activities of the datasets consist of the same energy expenditure value. All participants in the four studies were male, and of a healthy weight, therefore for simplicity body weight will not be considered at this stage.

The models are solved using the inbuilt MATLAB solver ODE45, based on explicit Runge-Kutta methods. The parameters are solved within MATLAB using the LSQNONLIN function. Initial parameter guesses are inputted into the function based on parameter values obtained in chapter 3, existing literature (Roy and Parker, 2007), (Cobelli et al., 1998), (Cobelli et al., 1982) and adjusted to allow for exercise induced effects.

5.4.1. Exercise at 30% of VO_2^{max}

In this section the models are implemented in MATLAB, setting $u_3 = 30$ and $T_d = 240$ to represent the individual working at 30% of their VO^{max}_2 for 240 minutes. The models are fitted to the data set obtained by Ahlborg et al. (1974), where individuals performed exercise following an overnight fast in a post-absorptive state.

The data set includes measurements for plasma glucose, insulin and glucagon, taken at 5 different time points, including the resting values, giving a total of 15 data points. Since the system consists of 13 unknown parameters a much greater number of data points would be required in order to give an accurate set of parameters for the model. This result is discussed later in the chapter.

Since the initial measurements from the study performed by Ahlborg et al. (1974) are taken after an overnight fast, the initial measurements from the data will be used for the model's initial and basal values for glucose, insulin and glucagon, i.e. $G_0 = G_b$, $E_0 = E_b$ and $I_0 = I_b$.

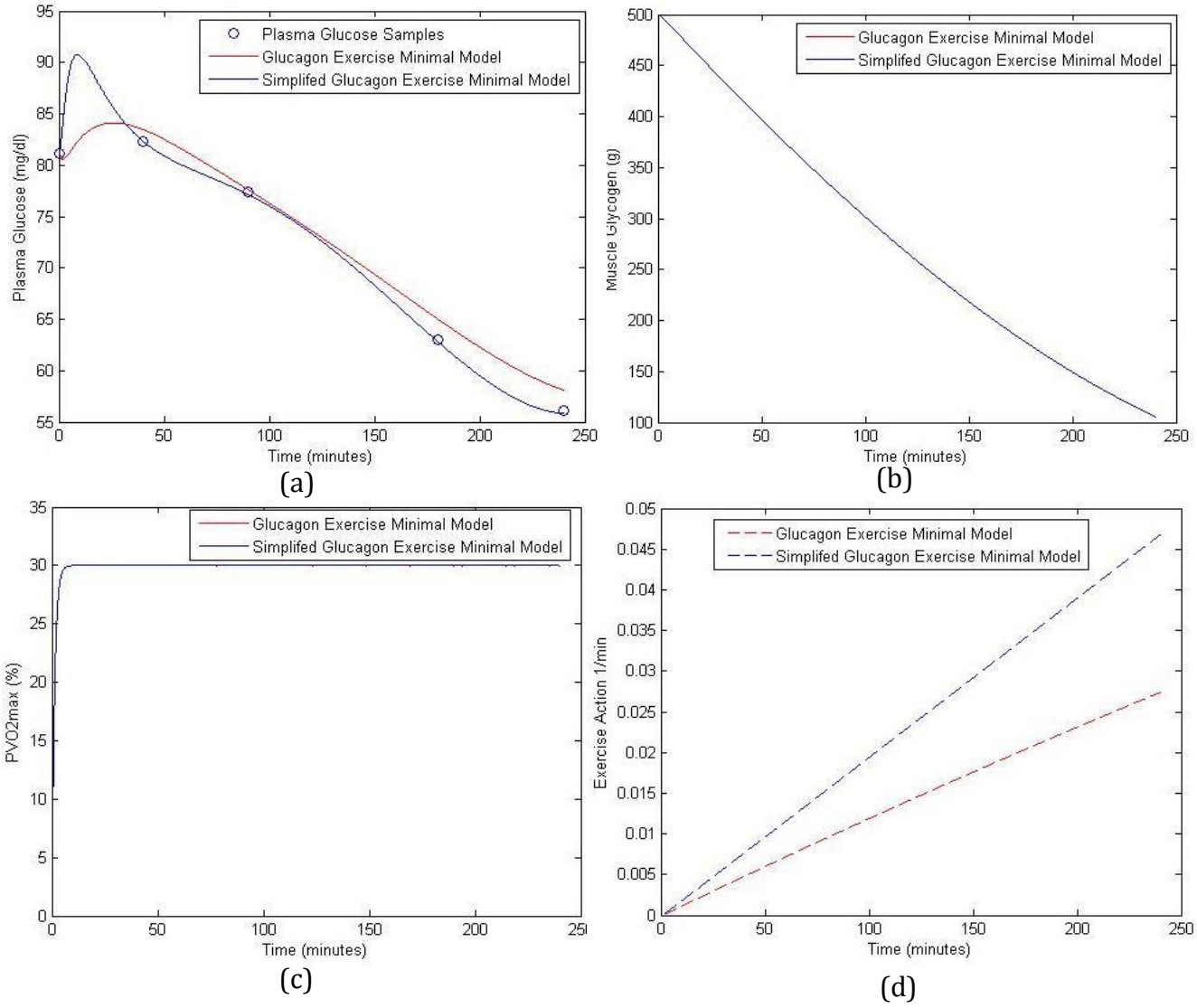


Figure 5.3: Exercise at 30% of PVO_2^{max} : G(t) against plasma glucose measurements, (a), Gly(t), (b), PVO_2^{max}(t), (c) and A(t), (d).

Figure 5.3 shows both models providing a good fit to the data set for plasma glucose (a), however the models show very different behaviour in the first 50 minutes of activity. The simulation for glucose in the Glucagon Exercise Minimal Model shows an initial fall in glucose levels, as the rate of glucose uptake increase to meet the increased demand for energy by the muscles, which is then met by an increase in HGP and glycogenolysis. Plasma glucose concentrations then gradually decrease with glycogen stores. In contrast, the Simplified Glucagon Exercise Minimal Model assumes an immediate increase in the concentration of glucose in the plasma, suggesting the onset of exercise is instantly met by an increase in glucose production, which then returns to basal and begins to decline as energy stores are depleted.

Both models predict a similar decrease in the amount of glycogen available throughout the duration of exercise. The models predict glycogen stores to decline to 20% of their starting values, which is very close to the physical actuality, as glycogen stores were depleted by approximately 75%, according to Ahlborg et al. (1974).

Both models show exercise activity increasing linearly as a function of exercise intensity and time (d). The Simplified Glucagon Exercise Minimal Model shows almost twice the amount of activity than the Glucagon Exercise Minimal Model, predicting the individual to be more sensitive to the effects of exercise.

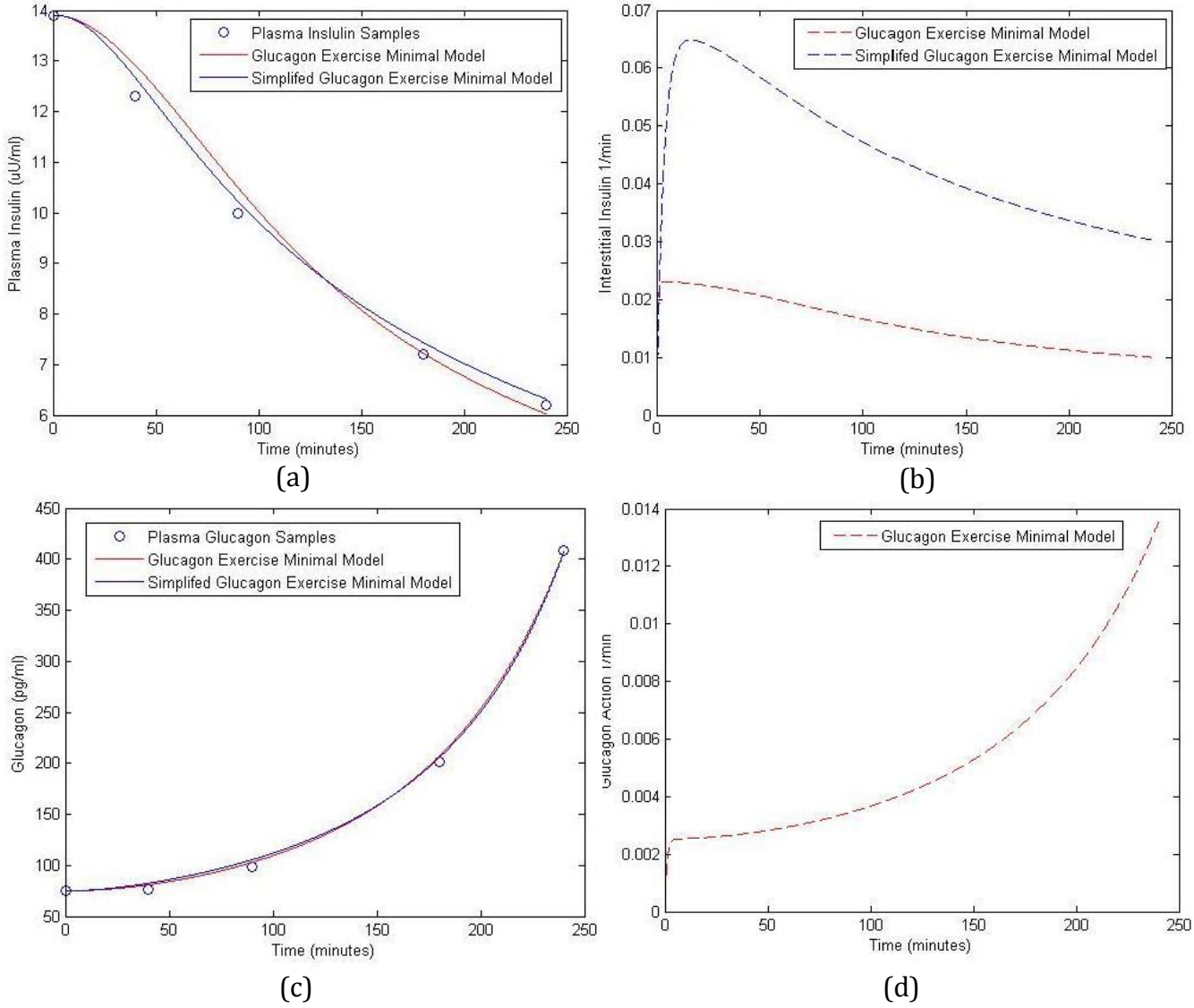


Figure 5.4: Exercise at 30% of PVO_2^{max}: I(t) against plasma insulin concentrations, (a), X(t), (b), E(t) against plasma glucagon concentrations, (c) and Y(t), (d).

Both models are capable of capturing the magnitude of the decline of plasma insulin concentrations (b); however, visually, the Simplified Glucagon Exercise Minimal Model provides a slightly better fit to the dataset. The Simplified Glucagon Exercise Minimal Model shows a greater amount of interstitial insulin activity than the Glucagon Exercise Minimal Model (b), suggesting a greater responsivity of the liver to insulin. Figure 5.4 (c) displays the accuracy of both models to fit the dataset of glucagon.

Table 5.7: Parameter results from simulations ran for both the Glucagon Exercise Minimal Model and the Linear Glucagon Exercise Minimal Model for 240 minutes of exercise at 30% of VO_2^{max}

Parameter GEMM	GEMM	Parameter SGEMM	SGEMM
$S_G = p_1$	0.017553609	p_1	0.00150000
p_2	2.239076769	p_2	0.30089987
p_3	0.003716462	p_3	0.00142961
p_4	0.018928669	p_4	0.03692484
p_5	$7.17288309 * 10^{-5}$	p_5	$4.1464406 * 10^{-4}$
p_6	0.98138568	-	-
p_7	$3.31033229 * 10^{-5}$	-	-
p_8	0.01758642	p_6	0.04036082
p_9	$2.56707631 * 10^{-6}$	p_7	$2.811859 * 10^{-12}$
-	-	P_8	0.10928015
p_{10}	0.10927865	p_9	$4.360198 * 10^{-14}$
p_{11}	$6.66091373 * 10^{-4}$	p_{10}	$6.4258065 * 10^{-6}$
p_{12}	$4.13286068 * 10^{-6}$	p_{11}	2.65330416
p_{13}	0.93794325	p_{12}	0.00503468
$S_I = \frac{p_3}{p_2}$	0.00165982	$S_I = \frac{p_3}{p_2}$	0.00475113
$S_E = \frac{p_7}{p_6}$	$3.37312064 * 10^{-5}$	-	-
$S_A = \frac{p_{12}}{p_{11}}$	0.006204645	$S_A = \frac{p_{10}}{p_9}$	$1.49667911 * 10^8$

In the both Glucagon Exercise Minimal Model and the Simplified Glucagon Exercise Minimal Model, the parameter values for glucose effectiveness, S_G, are lower than for the values obtained for the IVGTT models (tables 3.7 and 3.8). Exercise is typically reported to increase glucose effectiveness (Nishida et al., 2001) however there are a number of factors that may have influenced this result which will be further

discussed in section 5.5.

Table 5.7 shows higher values for both models in comparison to their values for insulin sensitivity, S_I, when simulated for an IVGTT (tables 3.7 and 3.8), which is confirmed by studies that have established that exercise increases insulin sensitivity (Richter et al., 1985), (Ross, 2003).

According to research, during exercise, there is an increase in sensitivity of the liver to glucagon during exercise (Bonjorn et al. 2002), (Adams, 2003). In comparison with the result from the IVGTT (table 3.7) the result from glucagon sensitivity, S_E, has in fact decreased. Despite this, comparing figures 5.4 and 3.7 it can be seen that the exercise model shows a much greater amount of glucagon activity acting on the system than in the IVGTT model. Therefore the likely cause for the exercise parameter value being lower than that of the IVGTT is that the term in Y(t) representing the increase in hepatic glucose production ability (p_7) is proportional to per unit of glucagon above baseline within the IVGTT Glucagon Minimal Model, whereas the exercise model is proportional to the total concentration of glucagon.

The new parameter exercise sensitivity, S_A, is introduced and is defined as the ability of the system to respond accordingly to the onset of exercise. The glucose regulatory system response in this model consists of the system's ability to decrease the concentration of insulin in the plasma, increase the concentration of plasma glucagon, increased muscle glucose uptake and glucose production (Goodwin, 2010). This value is expected to increase with exercise intensity and duration.

The Glucagon Exercise Minimal Model returns a value within a reasonable magnitude of the other key parameters listed, whereas the Glucagon Exercise Linear Minimal Model returns a significantly higher value, which appears mismatched in comparison with the other parameters.

5.4.2. Exercise at 40% of VO_2^{max}

The second dataset used to validate the models is from the experiment by Wolfe et al. (1984) where a group of healthy men took part in exercise at 40% of their VO_2^{max} for 60 minutes, following an overnight fast. Therefore the basal values will be fixed as the initial measurements, given the fact that the individuals were in the post absorptive state, and the exercise parameters will be fixed as $u_3 = 40$ and $T_{dur} = 60$.

As when fitting the models to the dataset in section 5.4.1, there are only 5 measurements taken for each of the physical quantities in the plasma to fit the models to, posing an issue with obtaining a good quality fit for the models and a unique set of parameter values.

Although the exercise intensity is slightly higher than the previous simulation in section 5.4.1, the exercise duration is significantly less. By estimating the total energy expenditure of both activities by calculating the products of the exercise activity and duration, it is presumed that the effects of exercise on the system will be significantly less than in the previous simulation.

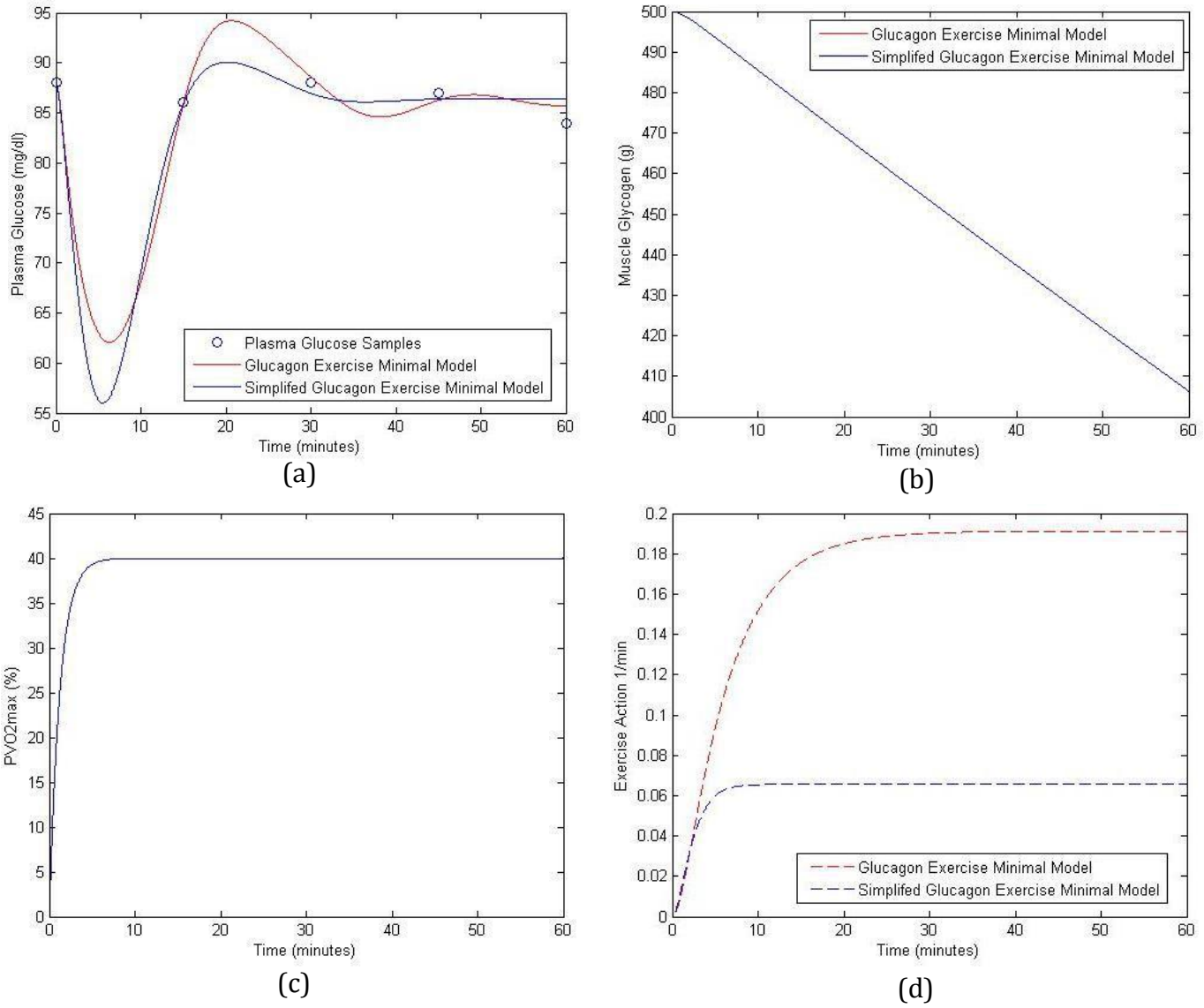


Figure 5.5: Exercise at 40% of VO_2^m: G(t) against plasma glucose measurements, G(t) (a), Gly(t), (b), PVO_2^{max}(t), (c) and A(t), (d).

Despite both models providing a fairly good fit to the dataset for plasma glucose levels, both anticipate a rapid fall in glucose levels within the first ten minutes of exercise.

Although quite often blood glucose concentrations fall as a result of a delay in the response of the glucose regulatory system to the onset of exercise, it is unlikely for levels to fall by such a significant amount. This is particularly true for the Simplified Glucagon Exercise Minimal Model, with predicts the individual to become severely hypoglycaemic and unlikely to be able to sustain exercise, thus making the Glucagon Exercise Minimal Model the preferred choice for glucose levels.

Both models predict the same amount of decline for muscle glycogen, show stores to only deplete by a quarter of the starting amount. Since the total energy expenditure is low it would be unlikely that a great amount would be utilised.

Both models demonstrate a greater amount of exercise activity than in comparison to the simulation for exercise at a lower intensity (see figure 5.3). For the simulation at 30% of VO_2^{max} exercise activity appeared to increase linearly with exercise intensity at time, where as in this simulation the level appears to reach a peak level corresponding to the activity of $PVO_2^{max}(t)$.

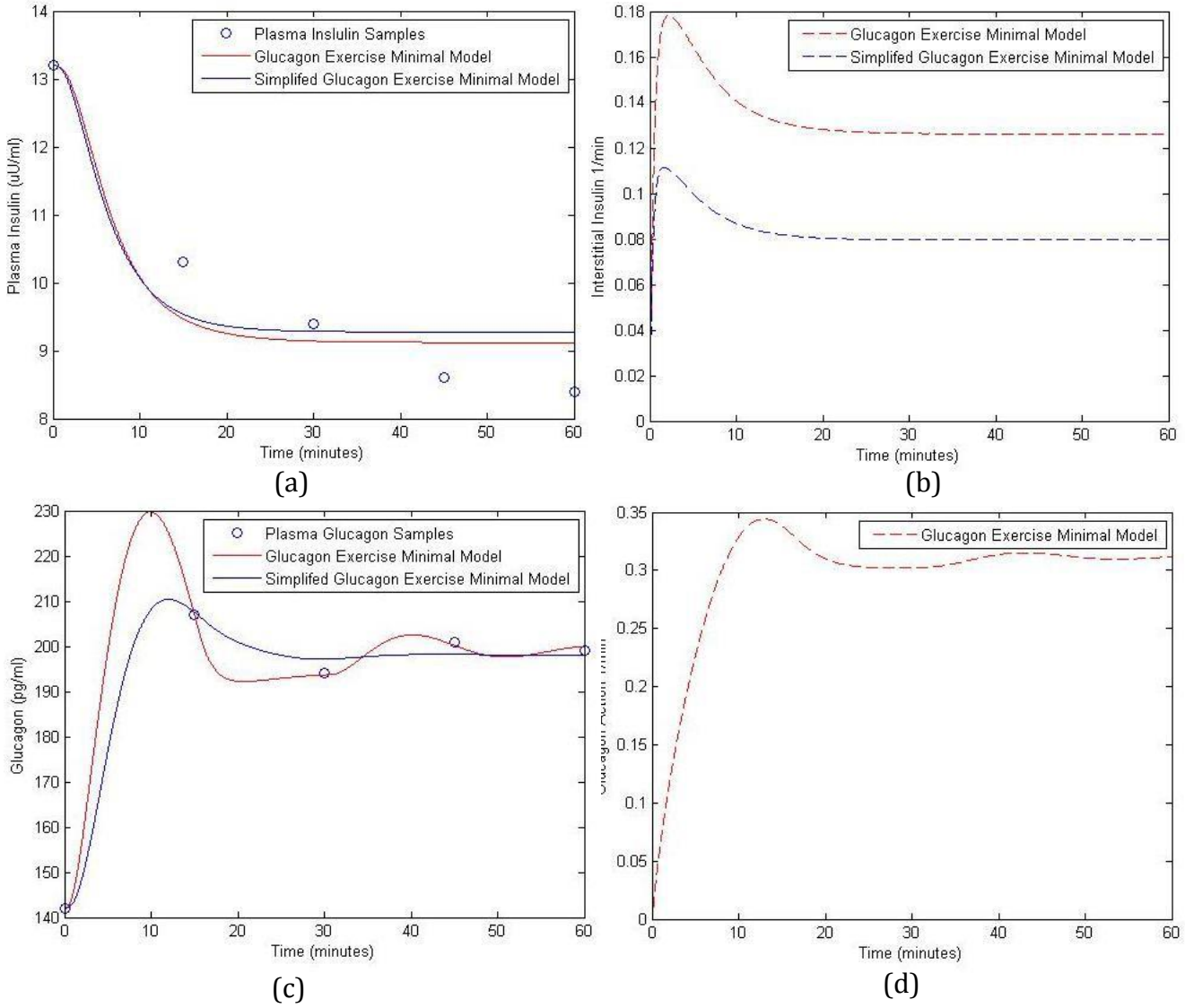


Figure 5.6: Exercise at 40% of VO_2^m: I(t) against plasma insulin concentrations, (a), X(t), (b), E(t) against plasma glucagon concentrations, (c) and Y(t), (d).

Both of the models predict plasma insulin levels (figure 5.6.a) to fall a little too quickly until it stabilises at what appears to be the minimum value. This behaviour correlates with exercise action, A(t), which ceases to increase as it reaches its ultimate level.

Neither of the models serve a good fit to the data set for plasma insulin, predicting the concentration falls much quicker in the initial 15 minutes and then assuming levels level out around 9.5 μU/ml rather than continuing to fall. In comparison with the model simulations for individuals exercising at 30% of their VO_2^{max}, both models show an increase in the amount of insulin activity, which is to be expected given the combination of the slightly higher intensity of the exercise being and performed and greater availability of insulin in the plasma.

The Glucagon Exercise Minimal Model provides an excellent fit to the data for glucagon, whereas the Simplified Glucagon Exercise Minimal Model still fits the data well, it misses the third and fourth points. Although the Simplified Glucagon Exercise Minimal Model fits the data well, it shows a very large spike in the first ten minutes, which is in response to the exaggerated fall in glucose seen in figure 5.5.a. The glucagon activity matches the behaviour of glucagon and is of a greater magnitude than at exercising at a lower intensity (figure 5.6.d), since the sensitivity of the liver to glucagon is magnified with increasing intensity.

Table 5.8: Parameter results from the simulations for both the Glucagon Exercise Minimal Model and the Simplified Glucagon Exercise Minimal Model for 60 minutes of exercise at 40% of VO_2^m.

Parameter GEMM	**Value**	**Parameter SGEMM**	**Value**
p_1	$9.82210456 * 10^{-7}$	p_1	$1.294901545 * 10^{-4}$
p_2	2.174472150	p_2	3.046685906
p_3	0.030060071	p_3	0.026127559
p_4	0.427363226	p_4	0.155124835
p_5	$3.10209295 * 10^{-7}$	p_5	$2.03958405 * 10^{-7}$
p_6	0.351946257	-	-
p_7	$5.50234639 * 10^{-4}$	-	-
p_8	0.710810527	p_6	0.238400979
p_9	1.374827718	p_7	1.374827718
-	-	P_8	0.223552393
p_{10}	0.061870951	p_9	0.061870951
p_{11}	0.183857888	p_{10}	0.814572420
p_{12}	$8.78558488 * 10^{-4}$	p_{11}	0.001336112
p_{13}	0.314711184	p_{12}	0.362639165
$S_I = \frac{p_3}{p_2}$	0.013824077	$S_I = \frac{p_3}{p_2}$	0.008575731
$S_E = \frac{p_7}{p_6}$	0.001563405	-	-
$S_A = \frac{p_{12}}{p_{11}}$	0.004778465	$S_A = \frac{p_{10}}{p_9}$	13.16566828

Both models return very low values for glucose effectiveness in comparison to the IVGTT models and the exercise simulations where $u_3 = 30$ (see tables 3.7, 3.10 and 5.6). This result was unexpected, given the extent of research that has found glucose effectiveness to increase with exercise (Nishida et al., 2001). For the Glucagon Exercise Minimal Model it is possible that the low value of glucose is due to the marked increase in both glucagon and insulin sensitivity. These outcomes are discussed fully with the other parameter results in section 5.5.

The increase in insulin sensitivity for both models in comparison to the previous results for the $PVO_2^{max} = 30$ indicate a higher level of insulin dependent glucose uptake and generally better health (Insulin Sensitivity, no date), which, in view of the measurements being taken from multiple people, could be down to individual variation.

The result for insulin sensitivity, S_I, also deviates from expectations. It has been established that the greater the amount of glycogen depleted in a bout of exercise, the greater the increase in insulin sensitivity (Colberg, 2007). Therefore since more glycogen was depleted for the simulation where an individual was exercising at 30% of their VO_2^{max}, the result would suggest that insulin sensitivity ought to be lower in this simulation. Due to the fact that the two datasets were from different individuals, it is likely that the participants in the study by Wolfe et al. (1984) had a higher sensitivity to insulin than those of the study performed by Ahlborg et al. (1974).

Exercise sensitivity has slightly decreased in value for the Glucagon Exercise Minimal Model, which, despite an increased exercise intensity, seems reasonable given that the duration of exercise for this dataset was a quarter of that for the measurements taken during exercise where $PVO_2^{max} = 30$. The value for the Linear Glucagon Exercise Minimal Model has also decreased, and is of a significantly lower magnitude than of the previous simulation.

5.4.3. Exercise at 58% of VO_2^{max}

The third data set the models are validated against is taken from the results from Ahlborg and Felig (1982). In this experiment a group of healthy, non-diabetic men took part in 210 minutes of exercise at 58% of their VO_2^{max} following a 12-14 hour overnight fast. Thus the initial measurements for glucose, insulin and glucagon were fixed as the basal values, with the exercise parameters set as $u_3 = 58$ and $T_{dur} = 210$.

This dataset consists of 6 data points available for each concentration within the plasma, which, although is three more points than offered by the previous datasets, is still an insufficient number to obtain a parameter set with narrow confidence intervals.

Since this simulation is of a higher intensity than both of the previous simulations and is for a considerable duration, the effects of exercise on the system are expected to be considerably greater than previously seen.

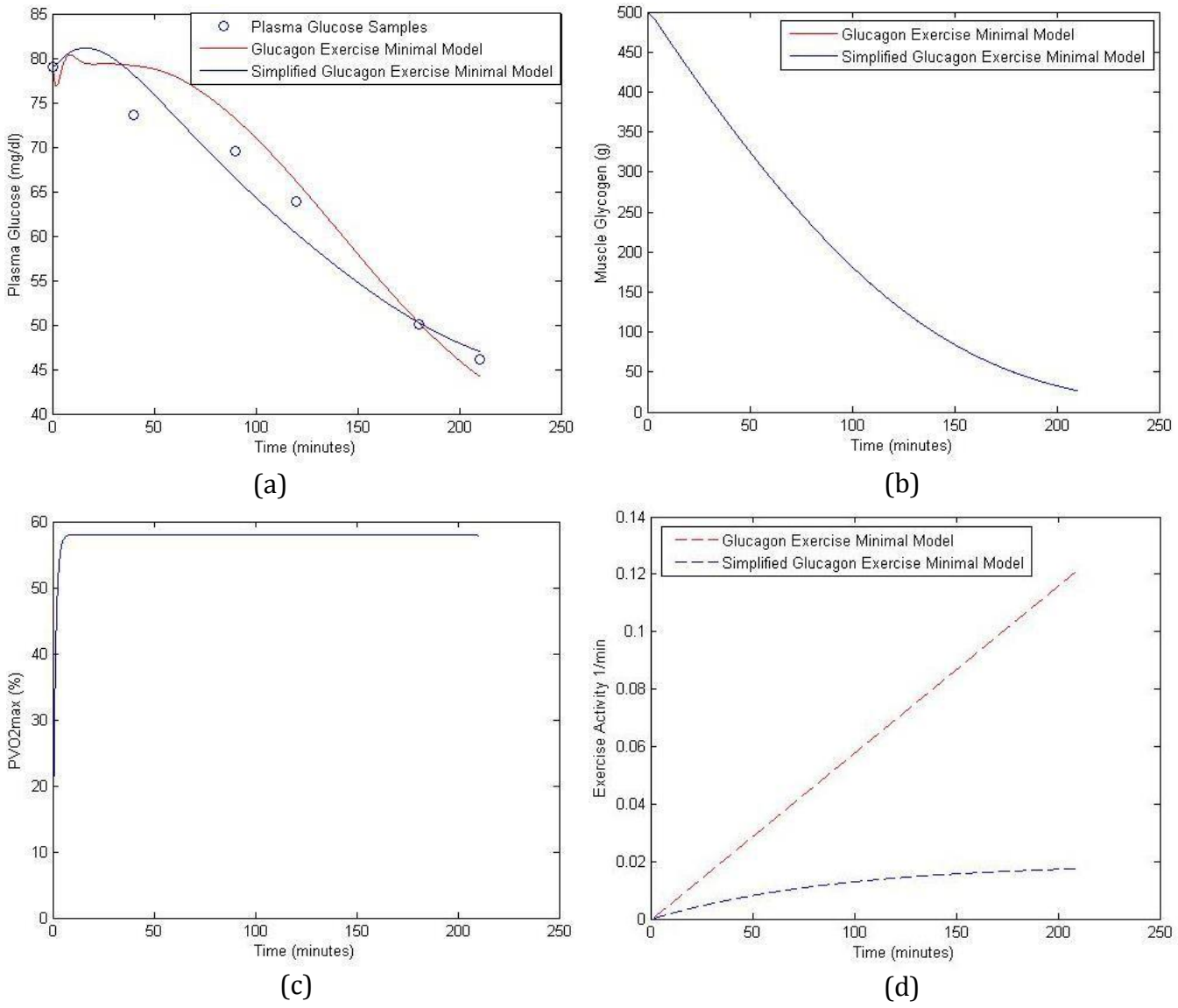


Figure 5.7: Exercise at 58% of VO_2^{max}: G(t) against plasma glucose measurements, G(t) (a), Gly(t) (b), PVO_2^{max} (c), and A(t) (d).

The two models show different behaviour for plasma glucose levels. The Simplified Glucagon Exercise Minimal Model shows more continuous behaviour, predicting levels to increase rapidly as a result of the model's overestimation of glucagon levels, then decline too quickly, overestimating the glucose concentration for a large part of the exercise duration. The Glucagon Exercise Minimal Model shows unstable as the hormones adjust to the onset of exercise, before settling into a gradual decline as glycogen stores become depleted.

Both models predict a fast decline in glycogen stores, which become entirely depleted by the end of the duration of activity. This suggests that, out of the three exercise protocols so far, this is the most effective for improving the diabetic state. This verdict is based on the results of the research by Colberg (2007) and Kang et al. (1996) who

found a longer improvement in insulin sensitivity was related to the greater the amount of glycogen burned during a bout of activity.

The Glucagon Exercise Minimal Model shows significantly greater levels of exercise activity out of the two. It displays a greater amount of activity than the protocol for 30% as expected but less than 40% which appears quite unconventional, given the increase in intensity and exercise duration. The Simplified Glucagon Exercise Minimal Model shows less exercise activity than both of the previous simulations, a result that deviates from the predicted outcome based on research, thus giving some doubt to the reliability of the model.

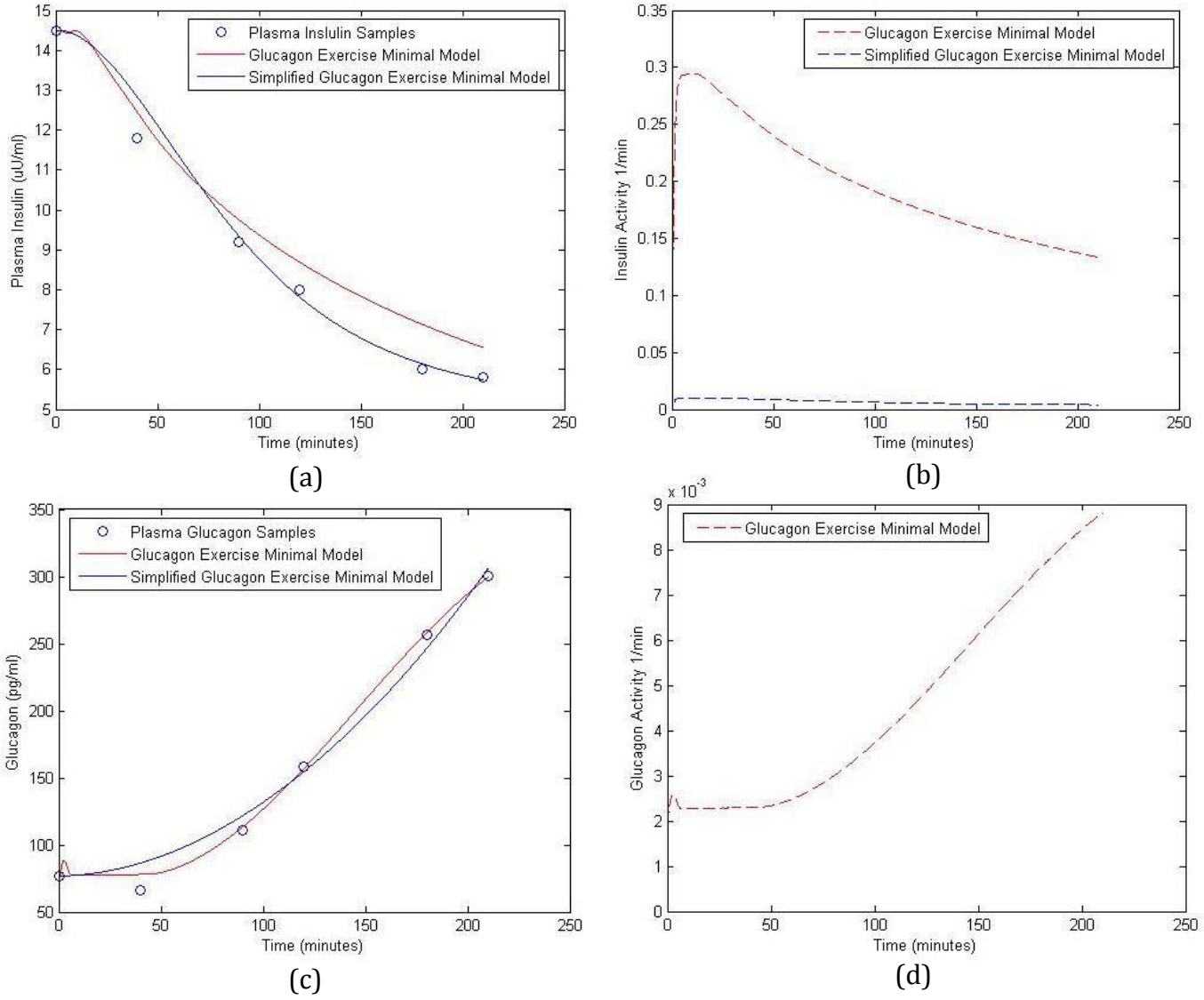


Figure 5.8: Exercise at 58% of VO_2^{max}: I(t) against plasma insulin concentrations, (a), X(t), (b), E(t) against plasma glucagon concentrations, (c) and Y(t), (d).

The results for plasma insulin clearly show the Simplified Glucagon Exercise Minimal Model to provide the better fit to the data of the two, since the Glucagon Exercise Minimal Model underestimates the rate of decline in plasma insulin levels.

However the Simplified Glucagon Exercise Minimal Model has a very low level of insulin activity in comparison with the simulations for exercise of 30% and 40% of VO_2^{max} than at 58% of VO_2^{max}, which is not expected, since, as previously

mentioned, insulin sensitivity has been observed to increase with decreasing glycogen levels and increased energy expenditure (Verkerke et al., 2015). This simulation has shown glycogen levels to deplete at a faster rate than previous simulations; therefore insulin activity should follow insulin sensitivity be the greatest

for this simulation. The Glucagon Exercise Minimal Model however does meet this

expectation, as there is a slightly higher amount of activity than demonstrated at 30% of and significantly more than at 40%.

The Glucagon Exercise Minimal Model provides a notably better fit to the plasma glucagon measurements than the Simplifed Glucagon Exercise Minimal Model, which rises too quickly and is responsible for the initial increment in plasma glucose.

Table 5.9: Parameter results from simulations for both the Glucagon Exercise Minimal Model and the Simplified Glucagon Exercise Minimal Model for 210 minutes of exercise at 58% of VO_2^{max}.

Parameter GEMM	**Value**	**Parameter SGEMM**	**Value**
$S_G = p_1$	0.20550317	p_1	0.016411558
p_2	1.13046419	p_2	0.963873328
p_3	0.02299561	p_3	0.000679837
p_4	0.09800001	p_4	0.010277818
p_5	0.05600000	p_5	$7.87208 * 10^{-14}$
p_6	5.37961561	-	-
p_7	0.00015838	-	-
p_8	1.59847556	p_6	0.161251435
p_9	9.20837923	p_7	0.016193108
p_{10}	0.09947311	p_8	0.001037968
p_{11}	0.00000188	p_9	0.099488025
p_{12}	0.00001003	p_{10}	0.010979608
p_{13}	6.40031140	p_{11}	0.000003678
-	0.02034174	p_{12}	2.681901231
$S_I = \frac{p_3}{p_2}$	0.00002944	$S_I = \frac{p_3}{p_2}$	0.000705317
$S_E = \frac{p_7}{p_6}$	5.32583804	-	-
$S_A = \frac{p_{12}}{p_{11}}$	0.20550317	$S_A = \frac{p_{12}}{p_{11}}$	0.110361102

The values for glucose effectiveness for both the Glucagon Exercise Minimal Model and the Simplified Glucagon Exercise Minimal Model have increased significantly in comparison to the values returned for the models by any of the other simulations for exercise or the IVGTT. This result suggests long durations of exercise at a moderate exercise intensity significantly increase glucose effectiveness.

The value of insulin sensitivity for both of the models has decreased in comparison to the values for the models from the previous simulations of exercise at lower

intensities. This is an unexpected result, given the greater amount of energy expenditure in this simulation. This result suggests that the data obtained from this study was from an individual with a higher insulin resistance than the previous two.

Glucagon sensitivity has increased a considerable amount from the previous simulations, a result which is expected given the high intensity and prolonged duration of the exercise. This result is likely to be an adaptation of the liver to prolonged exercise in order to avoid hypoglycaemia. If this value did not decrease post workout, combined with the low value for insulin sensitivity the individual would be at a risk of experiencing hyperglycaemia.

For the Glucagon Exercise Minimal Model, exercise sensitivity is at its highest value, and shows a trend of increasing with total energy expenditure. This is a positive result, as it is what would have been expected for if all of the data had been obtained from the same individual. The Simplified Glucagon Exercise Minimal Model shows a lower value for exercise activity, particularly in comparison to the previous simulation (see table 5.8). At present there appears to be no relationship between exercise sensitivity and energy expenditure, intensity or duration.

5.4.4. Exercise at 70% of VO_2^{max}

The final dataset used to validate the model is from Campbell et al. (2014) and consist of the glucose and hormone concentrations within the plasma being measured four times over 45 minutes whilst the patients are exercising at approximately 70% of their VO_2^{max}. The individuals all had type 1 diabetes, however they had received insulin treatments, and therefore the model will not be changed and it will be assumed that the insulin present in the blood was the result of pancreatic secretion. Patients took part in the evening, and were not in the fasted state; therefore the initial conditions will not be starting at the basal levels.

Since the dataset was obtained from individuals with type 1 diabetes, it is unlikely that the two models in this chapter will present a good fit to the plasma insulin measurements, as the equations for insulin (5.11 and 5.19) assumes insulin production and normal beta cell functionality. A model is introduced in chapter 6 that assumes type 1 diabetes and requires an input function for exogenous insulin, thus is expected to give a better fit to the data.

The patients who took part in the study by Campbell at el. (2014) were considered to be healthy and not known to have any diabetes related complications normal gluco-regulatory responses will be assumed and no changes will be made to the models.

Despite the exercise duration being shorter than the previous simulations, since the exercise intensity is fairly high it is expected that this exercise protocol ought to have a significant impact on the glucose regulatory system.

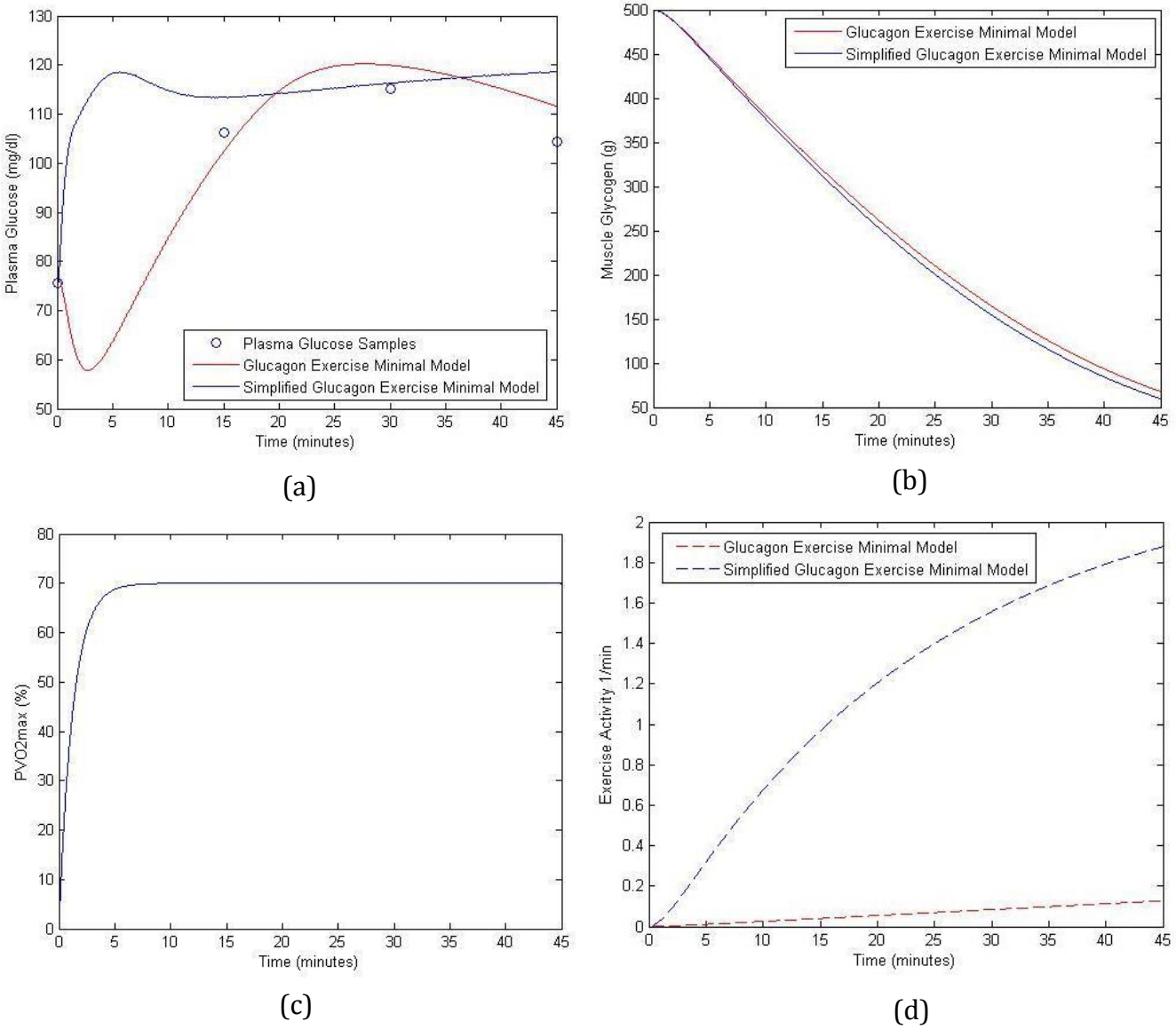


Figure 5.9: Exercise at 70% of VO_2^{max}: G(t) against plasma insulin concentrations, (a), $PVO_2^{max}(t)$, (b), E(t) against plasma glucagon concentrations, (c) and A(t), (d).

The Glucagon Exercise Minimal Model provides the better fit of the two models to the dataset. It predicts an initial fall in glucose concentrations as the onset of exercise increases the demand for glucose as fuel by the working muscles. Research shows that, during the first fifteen minutes of exercise, fuel for the working muscles mostly comes from glucose within either the blood stream or stored as muscle glycogen (Giles, 2016). Glucose levels then rise as the glucagon concentration increases and subsequently cause an increase in the rate HGP. The Simplified Glucagon Exercise Minimal Model predicts that glucose production will rise immediately, which is likely to be a result of the exaggerated rise it anticipates for plasma glucagon levels, as shown in figure 5.10.a.

Both models show a similar rate for the depletions of glycogen stores, with the Simplified Glucagon Exercise Minimal Model falling slightly lower.

The Simplified Glucagon Exercise Minimal shows a much greater level of exercise activity than the Glucagon Exercise Minimal Model. Although it is not unlikely that this simulation would result in the highest levels of exercise activity, the result given by the Simplified Glucagon Exercise Minimal is of a far greater magnitude than any of the previous simulations, making its physiological accuracy questionable.

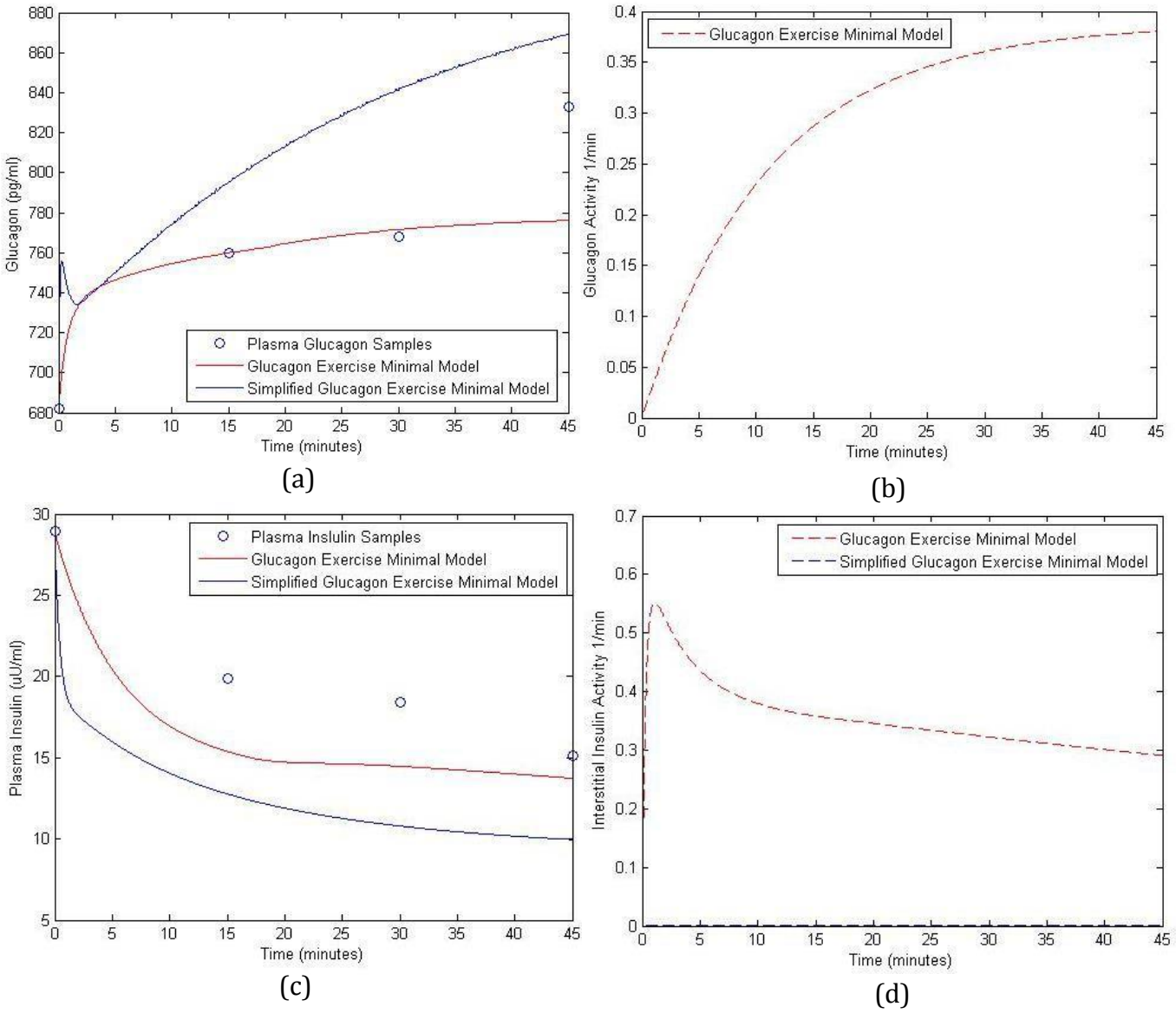


Figure 5.10: Exercise at 70% of VO_2^{max}: E(t) against plasma glucagon concentrations, (a), Y(t), (b), I(t) against plasma insulin concentrations, (c) and X(t), (d).

The Glucagon Exercise Minimal Model provides a much better fit to the dataset for plasma glucagon measurements than the Simplified Glucagon Exercise Minimal Model. It shows levels rise quickly accordingly with the onset of exercise and fall in glucose levels (figure 5.9.a) and then remain at a consistent elevated level for the remaining duration of exercise. The Simplified Glucagon Exercise Minimal Model predicts unusual behaviour, show a sharp rise then fall in levels before continually rising, overshooting all data points. From figure 5.9.d it is clear to see that the elevated level of exercise activity for the Simplified Glucagon Exercise Minimal Model is responsible for the excess of glucagon in the plasma.

Although neither of the models provides a good fit to the insulin data, clearly the Glucagon Exercise Minimal Model is the better of the two. The models were not

expected to fit the data well, since they both simulate a healthy patient, whereas this data was collect from type 1 diabetic individuals, administering exogenous insulin. It is known that exogenously delivered insulin is not subject to normal physiological feedback regulation (McCrimmon and Sherwin, 2010) as is assumed by equation (5.11) in the model, which is likely to be the cause of the poor data fit.

Table 5.10: Parameter results from simulations for both the Glucagon Exercise Minimal Model and the Simplified Glucagon Exercise Minimal Model for 45 minutes of exercise at 70% of VO_2^m.

Parameter GEMM	**Value**	**Parameter SGEMM**	**Value**
$S_G = p_1$	0.21299553	p_1	0.346341523
p_2	1.29778516	p_2	9.633789789
p_3	0.03443631	p_3	$1.173031 * 10^{-4}$
p_4	0.24788057	p_4	14.231816526
p_5	0.01799555	p_5	8.603068353
p_6	0.09630926	-	-
p_7	0.00004806	-	-
p_8	1.43637670	p_6	0.001000000
p_9	0.22328702	p_7	23.707465199
-	-	P_8	3.124506262
p_{10}	0.30186851	p_9	0.953347919
p_{11}	0.07182015	p_{10}	$4.189026 * 10^{-6}$
p_{12}	0.00009171	p_{11}	$8.169374 * 10^{-4}$
p_{13}	1.73064711	p_{12}	4.454932251
$S_I = \frac{p_3}{p_2}$	0.02653468	$S_I = \frac{p_3}{p_2}$	$1.217621 * 10^{-5}$
$S_E = \frac{p_7}{p_6}$	$4.989975 * 10^{-4}$	-	-
$S_A = \frac{p_{12}}{p_{11}}$	0.00127690	$S_A = \frac{p_{12}}{p_{11}}$	$4.394016 * 10^{-6}$

Both models return a high value for glucose effectiveness, which is to be expected given the high intensity and duration of exercise, resulting in an overall reasonably high level of energy expenditure.

The Glucagon Exercise Minimal Model returns a higher value for insulin sensitivity than all other simulations. Some evidence suggests that exercising at higher intensities achieve greater improvements in insulin sensitivity (Seals et al., 1984), (DiPietro et al., 2006). The result from the Glucagon Exercise Minimal Model confirms this finding; however more datasets will need to be collected for the model to be

fitted to in order to validate this conjecture with certainty. On the other hand the Simplified Glucagon Exercise Minimal Model returns a very low value for insulin sensitivity.

The Glucagon Exercise Minimal Model returns a lower value for glucagon sensitivity in comparison to the results from the IVGTT model and the simulations for exercise at both 40% and 58% of PVO_2^{max}. One aspect that may have influenced this result is that, research has shown that within a few years of diagnosis individuals with T1DM tend to fail to generate an adequate glucagon response (McCrimmon and Sherwin, 2010), which, since this dataset was obtained from participants with T1DM, may explain this result. Additionally, and most likely to be the case, is that this model assumes the increase of glucagon activity to be proportional to the total concentration of plasma glucagon, as opposed to the increase above the basal level as is assumed in the IVGTT model. The plasma measurements for glucagon in this data set are also markedly higher than in the previous data sets. Therefore with a greater amount of glucagon, a lower value of sensitivity will still have the same, if not larger, effects to the glucose regulatory system.

The Glucagon Exercise Minimal Model returns a moderately high value for exercise sensitivity in comparison to the other simulations whereas the Simplified Glucagon Exercise Minimal Model does not, returning an unexpectedly low value.

5.5. Discussion

In section 5.4 both of the models proposed in section 5.2 were simulated and fitted to the datasets obtained from four different studies on exercise, consisting of varying exercise intensities and durations. The parameter expectations and actual parameter results were briefly discussed and compared with the results for the IVGTT models in section 5.4. In this section an analysis of the parameters is given, comparing the values obtained from the simulations with each other, what the physiological implications of the values are in addition to possible factors that may have influenced the results. A comparison of the results for the key parameters is shown in table 5.12.

Before comparing the parameter values and discussing the implications it is to be noted that, since the datasets are not measurements all from the same individual, there is likely to be intra-individual variation in glucose regulation. This may have been the cause of some results differing from what was hypothesised.

Table 5.11: Comparison of the key parameters from the two exercise models for the four different exercise protocols.

Parameter	GEMM	SGEMM
30% of VO^{max}		
S_G	0.017553	0.001500
S_I	0.001659	0.004751
S_E	$3.3*10^{-5}$	-
S_A	0.017553	0.001500
40% of VO^{max}		
S_G	$9.82*10^{-7}$	1.2949010^{-4}
S_I	0.01382407	0.0085757
S_E	0.00156340	-
S_A	0.00477846	13.165668
58% of VO^{max}		
S_G	0.205503	0.0164115
S_I	$2.944* 10^{-5}$	0.0007053
S_E	5.325838	-
S_A	0.205503	0.1103611
70% of VO^{max}		
S_G	0.2129955	0.346341
S_I	0.0265346	$1.2176 * 10^{-5}$
S_E	0.0004990	-
S_A	0.0012769	$4.39 * 10^{-6}$

5.5.1. Glucose Effectiveness

In chapter 3 the acceptable range for glucose effectivenes, $S_G = p_1$, from an IVGTT was identified as $[0.8 - 3.8 * 10^{-2}]$, as defined by McDonald and co-workers (2000). All model simulations with the exception of where $PVO_2^m = 40$ lie within reasonable vicinity to this range, and typically increase with energy expenditure.

Exercise has been reported to increase glucose effectiveness (Nishida et al., 2001), (Sakamoto et al., 1999), as studies have found that, following a bout of exercise, glucose effectiveness would increase during an IVGTT in comparison to if individuals had been sedentary. However there are few studies that consider or attempt to measure glucose effectiveness during exercise.

Epinephrine is one of the main hormones whose concentrations markedly increase during exercise (Zouhal et al., 2008), and has been found to decreased glucose effectiveness significantly (Avagaro et al., 1996), It is possible that this may be an underlying cause of some values for glucose effectiveness being lower than expected. It is difficult to assess the effect of epinephrine without further study. This will be further discussed in chapter 7.

Glucose effectiveness is defined as the ability of hyperglycemia to promote glucose disposal at basal insulin (Nishida et al., 2001). Throughout the entire duration of exercise for all simulations, with the exception of where $PVO_2^{max} = 70$, the patients' plasma glucose concentrations remain fairly close to the basal levels and therefore disposal of excess glucose is not required. Given that the individual is not in a fed state it is difficult to evaluate of the ability of glucose to stimulate glucose uptake (Tonelli et al., 2005). Thus it is unlikely that the values of S_G during exercise give a true insight into the ability to dispose of glucose without the presence of insulin.

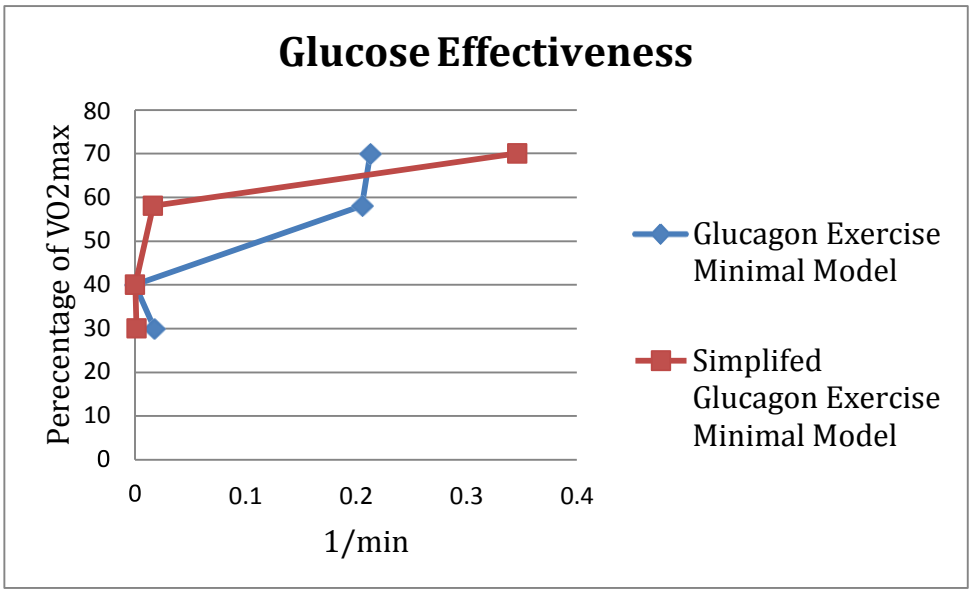


Figure 5.11: Comparison of Glucose Effectiveness for both exercise models for different durations and exercise intensities.

Figure 5.11 shows the relationship between glucose effectiveness and the four exercise protocols for both of the models. The Glucagon Exercise Minimal Model shows the value for the parameter to increase with intensity except for where $PVO_2^m = 40$, which is to be expected given the duration is much shorter than the simulations where $PVO_2^{max} = 30$, thus resulting in the lowest energy expenditure. The Simplified Glucagon Exercise Minimal Model does not predict this behaviour, and shows the value to continually rise with increasing intensity despite the differences in exercise duration.

5.5.2. Insulin Sensitivity

Referring to the ability of insulin stimulated glucose uptake (Lakshmi Kiran et al. 2010), insulin sensitivity, S_I, is a key parameter for analysing the diabetic state. The acceptable value for insulin sensitivity for a healthy person undertaking an IVGTT is given as approximately $5 * 10^{-4}$ (Pacini and Bergman, 1986).

One of the many benefits of exercise includes the fact that it increases insulin sensitivity (Richter et al., 1985), (Ross, 2003), (Borghouts and Keizer, 2000), (Holloszy, 2005). However, since the exercise models assume insulin activity to increase proportionally to the total amount of insulin in the plasma rather than the excess above the basal level, as is assumed in the IVGTT model, it is quite reasonable that the exercise models should return values that are lower than would have been expected. This change was made to the model as, if it had remained the same as in the IVGTT model, since there are low levels of insulin the model would assume that there was no insulin activity, which physiological is not true.

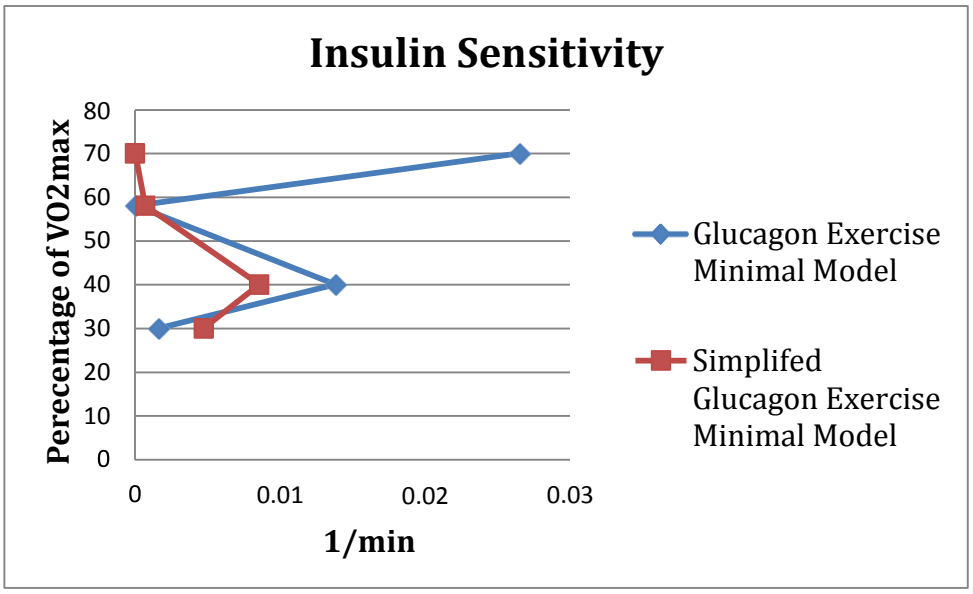


Figure 5.12: Comparison of Insulin Sensitivity for both exercise models for different durations and exercise intensities.

In figure 5.12 it can be seen that for Simplified Glucagon Exercise Minimal Model there is no trend for insulin sensitivity, giving the lowest values for the two protocols with the highest intensities and the highest value for the protocol with the lowest amount of energy expenditure, which is very unlikely. The Glucagon Exercise Minimal Model shows a much clearer trend, showing insulin sensitivity to increase with

intensity, as would be expected. The only anomaly is for $PVO_2^m = 58$, where for both models the value for insulin sensitivity is extremely low. It would suggest that the individual exercising was significantly more insulin resistant in comparison to the individuals of whom the other measurements were obtained from.

5.5.3. Glucagon Sensitivity

In 1985 Bonjorn et al. suggested that exercise was responsible for an increased sensitivity of the liver to glucagon. This has later been confirmed by Lavoie (2005), who found that an increase in glucagon receptor density occurred during both endurance exercise and periods of fasting, which appears to be an adaptation of the liver to enhance HGP responsiveness to glucagon, i.e. to increase glucagon sensitivity. In chapter 3 the Glucagon Minimal Model gave a value for glucagon sensitivity during the IVGTT to be $S_E = 0.001528$. Despite the fact that fasting increases glucagon sensitivity, it would be expected that, since at the beginning of the protocol the patient receives a large glucose bolus, thus inducing a fed state, glucagon sensitivity would be significantly lower than it would be for any of the exercise protocols. However since in the exercise models glucagon activity increases proportionally to the plasma glucagon concentration rather than the excess above the basal level, it is expected that the values may be slightly lower.

Often the effect of diabetes on glucagon regulation is overlooked, with treatment namely focusing on the insulin secretion abnormalities (Godoy-Matos, 2014). Individuals with T2DM may experience hyper secretion in the postprandial state and dysfunctional secretion in the fasting state (Khardori, 2013), therefore an abnormally low value for glucagon sensitivity during exercise may be seen as an indication of an impairment within the glucose regulatory system.

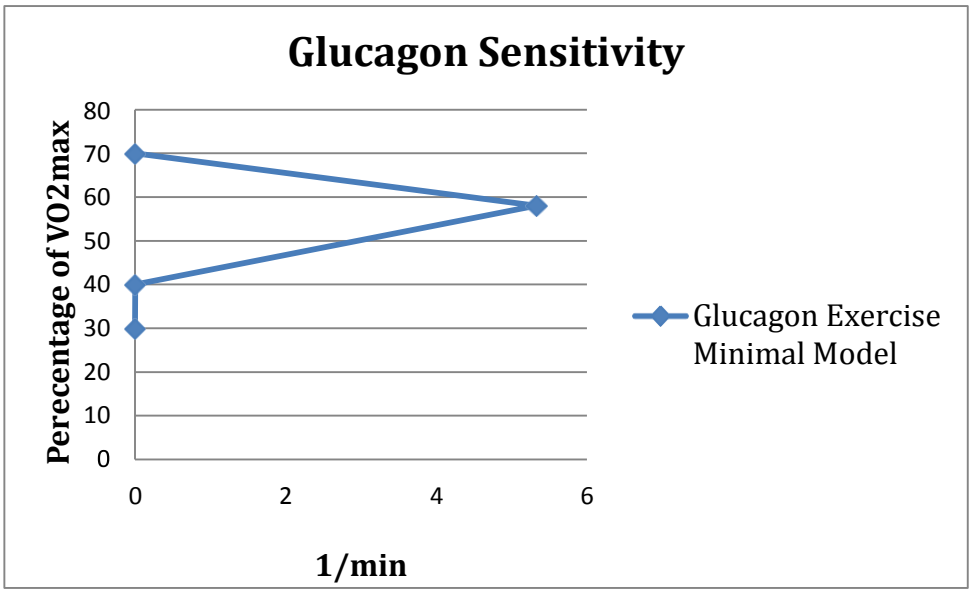


Figure 5.13: Comparison of Glucagon Sensitivity for the Glucagon Exercise Minimal Model for different durations and exercise intensities.

The Glucagon Exercise Minimal Model shows all values to be of a similar magnitude, with the exception of where $PVO_2^{max} = 58$, which returns a much higher value than the other three simulations. It is expected that glucagon sensitivity increases with increasing exercise duration and intensity, therefore since $PVO_2^{max} = 58$ resulted in the largest energy expenditure (produce of exercise intensity and duration), the parameter results are in keeping with the findings in literature.

5.5.4. Exercise Sensitivity

In this chapter a new parameter has been introduced referred to as exercise sensitivity,
S_A. This parameter is defined as the ability of the glucose regulatory system to respond and to act accordingly to the onset of exercise, i.e. to maintain homeostasis whilst meeting the increased demand for energy.

Since this is the first mathematical model to represent the effects of exercise in this manner, there are no existing values to compare the parameters to, however they should be within reasonable magnitude of the values for the other key parameters as listed in table 5.12.

It is not anticipated that a diabetic state ought to affect the individual's ability to respond directly to exercise. Since exercise stimulated glucose uptake acts through a separate signalling pathway to insulin dependent glucose uptake (Hayashi et al., 1997), it is considered to be normal even in those who suffer from insulin resistance and diabetes (Merry and McConell, 2009). Therefore, although some abnormalities are expected to occur during exercise, e.g. hyper- or hypoglycaemia, the value for exercise sensitivity is not expected to change significantly given the presence of the disease.

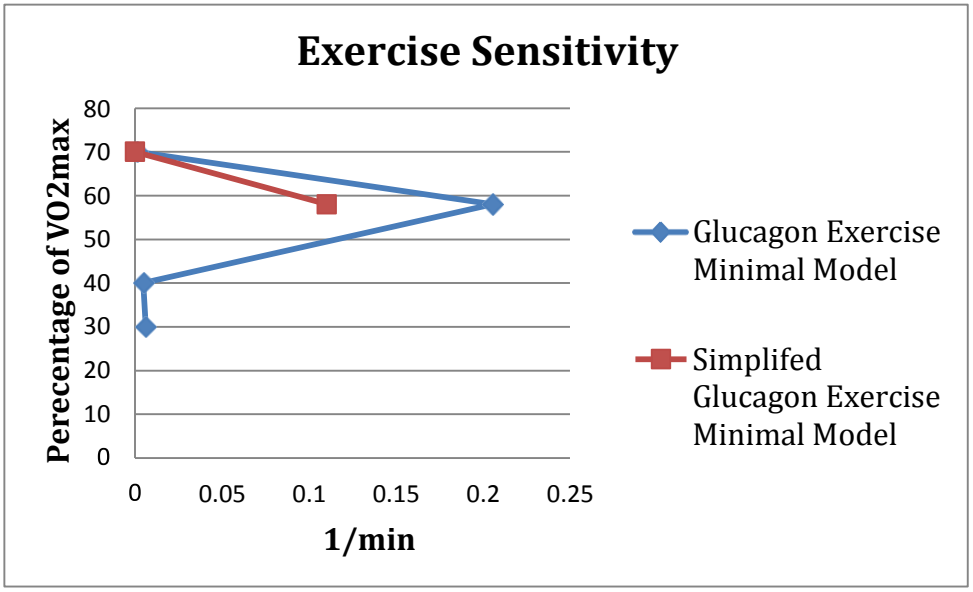


Figure 5.14: Comparison of the values for Exercise Sensitivity from both models for different durations and exercise intensities.

Figure 5.14 does not consider two of the parameter results for the Simplified Glucagon Exercise Minimal Model since the values are of a much larger magnitude than any of the other parameter values in these models, thus deemed unrealistic and inaccurate.

The Glucagon Exercise Minimal Model returns the highest value for where $PVO_2^{max} = 58$, which corresponds with expectations given that the individual was exercising for a long duration at a moderately high intensity, thus was most likely to have resulted in the highest amount of energy expenditure, confirming the models accuracy.

5.6. Summary

In this chapter two mathematical models have been proposed that are capable of accounting for the key processes responsible for blood glucose regulation during exercise.

The first model proposed, the Glucagon Exercise Minimal Model, modelled the effects of glucagon on glucose levels indirectly by introducing a non-linear variable that accounts of the level of glucagon induced activity within the system. The key parameter values, as shown in table 5.12 are all within physiological reasoning, with the values for both glucose effectiveness and insulin sensitivity lying within justifiable magnitude to the parameter values deemed acceptable for the IVGTT minimal model. Typically, the key parameters increased with increasing energy expenditure, which is estimated based on the work of Moore (2011) as a product of exercise duration and intensity.

The second model proposed, the Simplified Glucagon Exercise Minimal Model, assumed a linear relationship between the amount of glucagon in the plasma above baseline value and glucose. Although the model is advantageous in the sense it has a parameter and variable less than the Glucagon Exercise Minimal Model, the returned values for the key parameters do not correlate with each other, the hypotheses from literature nor are deemed as physiologically realistic.

Overall, the Glucagon Exercise Minimal Model provided the best fit to the data and the most physiologically accurate behaviour for concentrations of glucose and the two hormones in the plasma. Although it consistently provide a good fit, this is to be expected given the limited amount of data points available for the studies.

Research shows that the greater the amount of glycogen burned during a single exercise session, the greater the improvement for insulin sensitivity (Colberg, 2008), (Kang et al. 1996). The models show that the exercise protocol where $PVO_2^{max} = 70$ and $PVO_2^{max} = 58$ to be the best options for improving insulin sensitivity as they utilised the most glycogen. This is confirmed by the results of the Glucagon Exercise Minimal Model, which returned the highest value for insulin sensitivity of all of the simulations when $PVO_2^m = 70$. The model returns an unusually low value for $VO_2^{max} = 58$, however without further data to validate it is impossible to identify the cause of this result, and could simply due to individual variability.

Therefore the Glucagon Exercise Minimal Model was the best performing of the two models and will be extended in chapter 6 to consider an individual with T1DM diabetes.

Chapter 6 Insulin Infusion and Exercise

6.1. Introduction to Insulin Treatments for T1DM

As discussed in chapter 1, T1DM occurs when the pancreas is unable to produce any insulin; therefore patients are dependent on an exogenous supply to maintain glucose homeostasis. The aim of this chapter is to introduce a term into the models proposed to replicate insulin treatments. The response of plasma insulin concentrations to an exogenous supply varies, depending on the type of insulin treatment used. Figure 6.1 summarises the effect of varying treatments on insulin.

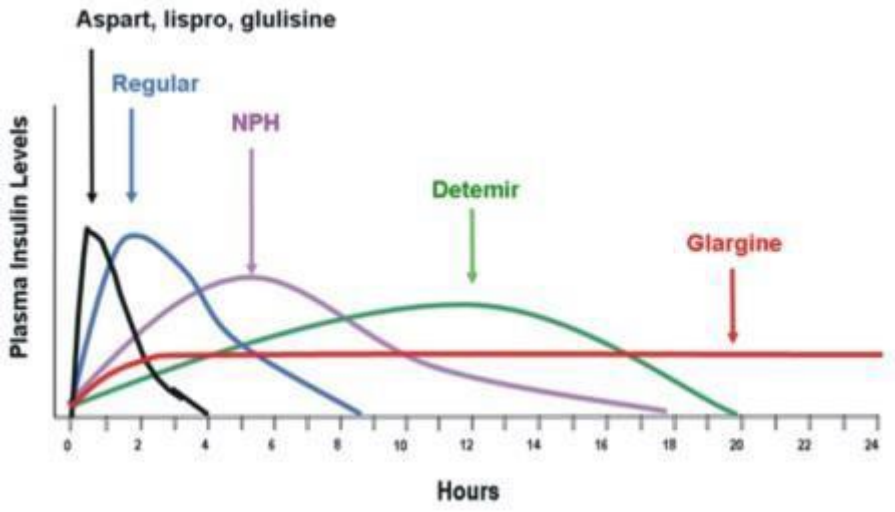


Figure 6.1: Different durations and onsets of various insulin treatments taken from Latif (2007).

Typically insulin treatments are classified as short, medium or long according on their action in time (Basov et al., 1999), as shown in table 6.1, adapted from Donner (2015), describing the pharmacokinetics of available insulins.

Table 6.1. Pharmacokinetics of insulins (Donner, 2015)

Insulin	Onset	Peak	Duration
Lispro	5-15 minutes	30-90 minutes	3-5 hours
Aspart	10-20 minutes	1-3 hours	3-5 hours
Regular Insulin	30-60 minutes	1-5 hours	6-10 hours
Buffered Regular Insulin	30-60 minutes	1-3 hours	8 hours
Lente	1-3 hours	6-14 hours	16-24 hours
NPH	1-2 hours	6-14 hours	16-24+ hours
Glargine	1.1 hours	None	24 hours
Ultralente	4-6 hours	8-20 hours	>24 hours

Therefore in order to develop a model capable of considering exogenous insulin, the mathematical term needs to be adaptable to allow for the different characteristics belonging to the various types of insulins, including different durations of the treatment, the size of the insulin dosage and the frequency of the administration.

Knowledge of the time action of insulins can help clinicians and patients to determine a suitable treatment plan and predict the effect of the treatment on the plasma over time. However, as for most aspects within the glucose regulatory system, insulin administration varies between patients and can be affected by a number of factors. McCulloch et al. (2016) list the external affecting factors to be the dose of insulin, the injection technique, the injection site and the time passed since opening the bottle, since the potency of insulin is noted to decrease over the following 30 days. In addition to the external factors relating to the administration of insulin, each individual will react differently to the treatments, due to variations in subcutaneous blood flow and levels of physical activity, which affect the diffusion conditions in the subcutaneous tissue (Hildebrandt, 1991).Developing a model that can account for and analyse the effects of such factors can assist the understanding and implementation of an effective treatment plan for individuals with T1DM.

6.2. Critical Review of Insulin Infusion Models

Basov et al. (1999) proposed a model that considers the effect of self-administered insulin, in order to help determine the required dosage and corresponding effects on glycaemia.

The term for insulin infusion is given mathematically as the following:

$$I_{exg} = \begin{cases} 0, & otherwise, \\ B * \sin(\pi * \frac{t}{T}), & t_0 \leq t \leq t_0 + T, \end{cases} \quad (6.1)$$

Where the constants have been defined by Sulston et al. (2007) as can be seen in table 6.2.

Table 6.2. Nomenclature for Basov's insulin infusion term

Parameter	Description
I_{Total}	Size of insulin dosage.
T	Duration of effectiveness of treatment, i.e. time taken for insulin treatment to
t_0	Time of administration
B	$\pi * \frac{I_{Total}}{2 * T}$
$\sin(\pi * \frac{t}{T})$	Representation of the behaviour of the infused insulin entering the plasma.

Although the model is simple to use and allows for the parameters to be adjusted for various insulin treatments there are drawbacks to the model proposed by Basov et al. (1999). The sine function is a continuous function that does not reach a natural end; therefore the function is forced to discontinue, which does not provide an accurate physiological representation and encounters issues when determining the long term behaviour of the system, since sine functions have no limit but simply oscillate between their minimum and maximum values.

Additionally, the model does not allow for different onset and clearance times, assuming that the insulin leaves the blood at the same rate at which it enters. This is demonstrated by a simulation of the minimal model, where the equation for insulin has been adapted to consider the sine term for exogenous insulin and the parameter values are set to those provided by Roy and Parker (2007) for a type 1 diabetic individual.

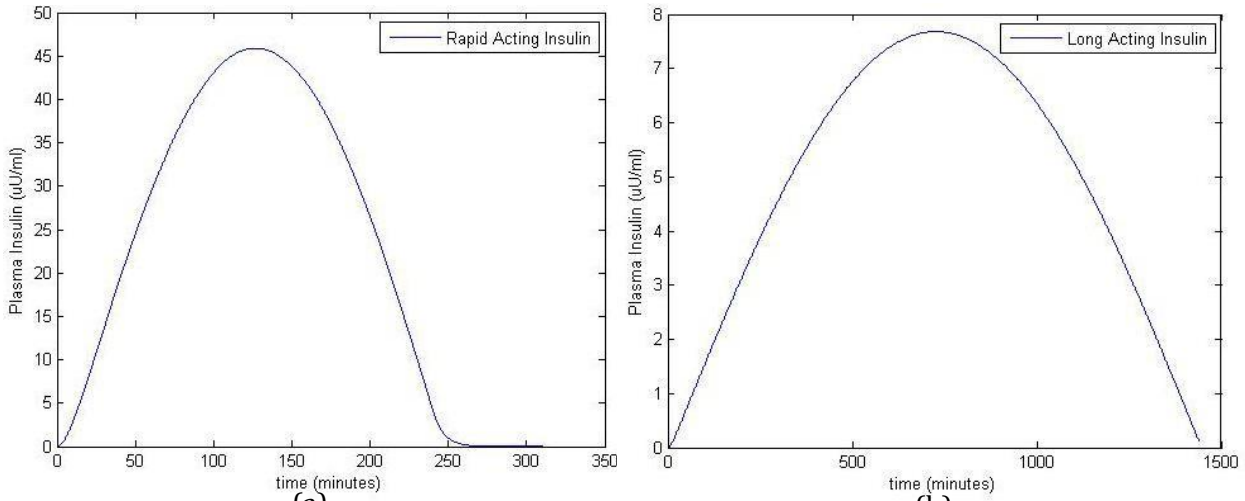


Figure 6.2. Simulation of the minimal model with the term proposed by Basov and co-workers for rapid (a) and long (b) acting exogenous insulin.

Other models to describe exogenous insulin administration include the model proposed by Li and Kuang (2009). Li and Kuang developed a system of differential equations to mimic the effects of rapid acting insulin, administered in hexameric form, which is then broken down into dimers, which are then broken down into monomers and absorbed into the bloodstream (Wuang et al. 2013). Their proposed system is as follows:

$$\frac{dH}{dt} = -p * \big(H(t) - q * D^3(t)\big), \tag{6.2}$$

$$\frac{dD}{dt} = p * \big(H(t) - q * D^3(t)\big) - b * \frac{D(t)}{1 + I(t)}, \tag{6.3}$$

$$\frac{dI}{dt} = r * b * \frac{D(t)}{1 + I(t)} - d_i * I(t), \tag{6.4}$$

where H is insulin analogue in hexameric form, D is insulin analogue in dimeric form and I is the plasma insulin concentration.

The model provided a good fit to experimental data and it possesses a unique globally asymptotically stable equilibrium. However, the system is significantly more complex in comparison to the term proposed by Basov et al. (1999), introducing 6 new quantities to model the effects in the system.

6.3. Model Formulation for Insulin Infusion

Since the aim of this thesis is to develop a mathematical model to predict blood glucose levels during exercise, the term for insulin administration will not go into the level of detail and complexity as Li and Kuang (2009) but will take a more simplified approach.

A term is proposed is designed to mimic the effects of administering insulin treatments:

$$I_{exg} = \alpha * (-\mathrm{e}^{-\pi * \frac{\mathrm{t}}{\mathrm{t_{on}}}} + e^{-\pi * \frac{t}{t_{deg}}}), \tag{6.5}$$

where t_{on} is the duration of the onset of the insulin treatment, $\mathrm{t_{deg}}$is the duration of the clearance from the plasma and α is the parameter that controls how the amount by which the treatment will increase the plasma insulin concentration.

6.3.1. Minimal Model and Insulin Infusion

The Minimal Model, equations (2.3-2.5), was adapted to simulate a type 1 diabetic patient. The first and second phase insulin secretion terms were removed and replaced with the term for insulin administration, I_{exg}, changing equation (2.5) to be the following:

$$\frac{dI}{dt} = -p_4 * I(t) + I_{exg}, \tag{6.6}$$

Notice that this new equation assumes no insulin secretion, implying a severe state of diabetes where the individual is entirely dependent on insulin treatments.

6.3.2. Exercise and Insulin Infusion

In chapter 5 two models were proposed to model the effects of exercise on the glucose regulatory system. Since the Exercise Glucagon Minimal Model provide the most accurate fit to the datasets it will be chosen to simulate exercise for type 1 diabetic patients.

Three of the datasets for exercise used to validate the models in this thesis (Ahlborg et al., 1974), (Ahlborg and Felig, 1984), (Wolfe et al., 1982) consider subjects exercising in the post absorptive state, following an overnight fast, therefore it is assumed that no rapid acting insulin is administered, as it is typically administered to accompany meals. Since a popular choice is to take long acting insulin (known as basal insulin) before a patient's bedtime (Diabetes.co.uk, 2012), it will be assumed for these three cases that the injection will have been administered t_{del} minutes before the individual started exercising. Therefore equation (6.5) will now become:

$$I_{exg} = \alpha * (-e^{-\pi * \frac{t+t_{del}}{t_{on}}} + e^{-\pi * \frac{t+t_{del}}{t_{deg}}}), \tag{6.7}$$

Adjusting equation (5.9) (see section 5.2) to mimic a type 1 diabetic patient exercising, the equation now becomes:

$$\frac{dI}{dt} = -p_4 * I(t) + I_{exgL} - I(t) * A(t), \tag{6.8}$$

Note that this equation also assumes an extreme form of diabetes where the pancreas secretes no insulin. This equation will be used for plasma insulin in the exercise model. For the dataset obtained by Campbell et al. (2014), the patients took part in exercise in the evening, in which they started 60 minutes after consuming a meal with a dose of rapid acting insulin. Therefore in order to replicate this protocol two insulin administrations will need to be considered; the long acting insulin that would have been administered the previous night, and the reduced rapid acting insulin that would have been administered 60 minutes prior to the exercise. Therefore the new equation for insulin becomes:

$$\frac{dI}{dt} = -p_4 * I(t) + I_{exgL} + I_{exgR} - I(t) * A(t), \tag{6.9}$$

where I_{exg} represents that long acting insulin and I_{ex} is the rapid acting insulin.

6.4. Model Analysis

The system is non-dimensionalized, as in section 5.3.1, however the variable for plasma insulin is now rescaled to give a variable with no units as $I = \frac{\tilde{I}}{\tau}$. Therefore the unitless exercise system for a type 1 diabetic patient is now given by:

$$\frac{d\tilde{G}}{dT} = -p_1 * \tau * \left(\tilde{G} - 1\right) + \tilde{G} * \left(\tilde{Y} - \tilde{X} - \tilde{A}\right) + \frac{p_{13} * p_{10} * Gl\tilde{y} * \widetilde{PVO_2^{max}}}{G_b * \left(\frac{1}{2} + Gl\tilde{y}\right)}, \tag{6.10}$$

$$\frac{d\tilde{X}}{dT} = -p_2 * \tilde{X} * \tau + p_3 * I_b * \tau^2 * \tilde{I}, \tag{6.11}$$

$$\frac{d\tilde{I}}{dT} = -p_4 * \tau * \tilde{I} + p_5 * \tau^2 * \left(-\mathrm{e}^{\frac{-\pi * \mathrm{T} * \tau + \mathrm{t_{del}}}{\mathrm{t_{on}}}} + e^{\frac{-\pi * \mathrm{T} * \tau - \mathrm{t}_{del}}{t_{deg}}}\right) - \tilde{A} * \tilde{I}, \tag{6.12}$$

$$\frac{d\tilde{Y}}{dT} = -p_b * \tilde{Y} * \tau + p_7 * E_b * \tau^2 * \tilde{E}, \tag{6.13}$$

$$\frac{d\tilde{E}}{dT} = -p_8 * \tau * \left(\tilde{E} - 1\right) + \frac{p_9 * G_b * \tau}{E_b} * \left(1 - \tilde{G}\right) + \tilde{A} * \tilde{E}, \tag{6.14}$$

$$\frac{dGl\tilde{y}}{dT} = -\frac{p_{10} * Gl\tilde{y} * \widetilde{PVO_2^{max}}}{Gly_b * \left(\frac{1}{2} + Gl\tilde{y}\right)} - p_{14} * \tau * (Gl\tilde{y} - 1), \tag{6.15}$$

$$\frac{d\widetilde{PVO_2^{max}}}{dT} = -0.8 * \widetilde{PVO_2^{max}} * \tau + 0.8 * \tau^2 * u_3, \tag{6.16}$$

$$\frac{d\tilde{A}}{dT} = -p_{11} * \tilde{A} * \tau + p_{12} * \tau * \widetilde{PVO_2^{max}}, \tag{6.17}$$

By setting $\tau = \frac{1}{p_4}$ the system is rescaled for insulin disappearance and is rewritten as:

$$\frac{d\tilde{G}}{dT} = -\widetilde{p_1} * \left(\tilde{G} - 1\right) + \tilde{G} * \left(\tilde{Y} - \tilde{X} - \tilde{A}\right) + \frac{\widetilde{p_{13}} * Gl\tilde{y} * \widetilde{PVO_2^{max}}}{\left(\frac{1}{2} + Gl\tilde{y}\right)}, \tag{6.18}$$

$$\frac{d\tilde{X}}{dT} = -\widetilde{p_2} * \tilde{X} + p_3 * I_b * \tau^2 * \tilde{I}, \tag{6.19}$$

$$\frac{d\tilde{I}}{dT} = -(\tilde{I} - 1) + \widetilde{p_5} * \left(-\mathrm{e}^{\frac{-\pi * \mathrm{T} * \tau + \mathrm{t_{del}}}{\mathrm{t_{on}}}} + e^{\frac{-\pi * \mathrm{T} * \tau - \mathrm{t}_{del}}{t_{deg}}} \right) - \tilde{I} * \tilde{A}, \tag{6.20}$$

$$\frac{d\tilde{Y}}{dT} = -\widetilde{p_6} * \tilde{Y} + \widetilde{p_7} * \tilde{E}, \tag{6.21}$$

$$\frac{d\tilde{E}}{dT} = -\widetilde{p_8} * \left(\tilde{E} - 1\right) + \widetilde{p_9} * \left(1 - \tilde{G}\right) + \tilde{A} * \tilde{E}, \tag{6.22}$$

$$\frac{dGl\tilde{y}}{dT} = -\frac{\widetilde{p_{10}} * Gl\tilde{y} * \widetilde{PVO_2^{max}}}{\left(\frac{1}{2} + Gl\tilde{y}\right)} - \widetilde{p_{14}} * (Gl\tilde{y} - 1), \tag{6.23}$$

$$\frac{d\widetilde{PVO_2^{max}}}{dT} = -0.8 * \frac{\widetilde{PVO_2^{max}}}{p_4} + \frac{0.8 * u_3}{p_4^2}, \tag{6.24}$$

$$\frac{d\tilde{A}}{dT} = -\widetilde{p_{11}} * \tilde{A} + \widetilde{p_{12}} * \widetilde{PVO_2^{max}}, \tag{6.25}$$

where the unitless parameters are defined as:

$\widetilde{p_1} = \frac{p_1}{p_4}, \widetilde{p_2} = \frac{p_2}{p_4}, \widetilde{p_3} = \frac{p_3 * I_b}{p_4^2}, \widetilde{p_5} = \frac{p_5}{p_4^2}, \widetilde{p_6} = \frac{p_6}{p_4}, \widetilde{p_7} = \frac{p_{7*E_b}}{p_4^2}, \widetilde{p_8} = \frac{p_2}{p_4},$
$\widetilde{p_9} = \frac{p_9 * G_b}{p_4 * E_b}, \widetilde{p_{10}} = \frac{p_{10}}{Gly_b}, \widetilde{p_{11}} = \frac{p_{11}}{p_4}, \widetilde{p_{12}} = \frac{p_{12}}{p_4}, p_{1\tilde{3}} = p_{13} * \frac{p_{10}}{G_b}$ and $\widetilde{p_{14}} = \frac{p_{14}}{p_4}$.

The initial conditions then become

$$\tilde{G}(0) = \frac{G_b}{G_b} = 1, \tilde{X}(0) = 0, \tilde{I}(0) = \frac{I_0}{p_4}, \tilde{Y}(0) = 0, \tilde{E}(0) = \frac{E_b}{E_b} = 1,$$
$$Gl\tilde{y}(0) = \frac{Gly_b}{Gly_b} = 1, \widetilde{PVO_2^{max}}(0) = 0 \text{ and } \tilde{A}(0) = 0.$$

Examining the long term behaviour of the system it becomes clear that the new stationary point for the dimensional exercise model becomes

$$\lim t \to \infty f(G(t), X(t), I(t), Y(t), E(t), Gly(t), PVO_2^{max}(t), A(t)$$

$$= (G_b, 0, 0, \frac{p_7}{p_6} E_b, E_b, Gly_b, 0, 0)$$

therefore in non-dimensional terms this becomes $(1,0,0, \frac{p_8}{p_6}, 1,1,0,0)$.

The Jacobian matrix evaluated at the critical point is given as:

$$J_3 = \begin{bmatrix} -\tilde{p_1} - \frac{\widetilde{p_2}}{\widetilde{p_2}} + \frac{\widetilde{p_7}}{\widetilde{p_6}} & -1 & 0 & 1 & 0 & 0 & 2 * \frac{\widetilde{p_{13}}}{3} & -1 \\ 0 & -\widetilde{p_2} & \widetilde{p_3} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & 0 & 0 & 0 & 0 & -1 \\ 0 & 0 & 0 & -\widetilde{p_6} & \widetilde{p_7} & 0 & 0 & 0 \\ -\widetilde{p_9} & 0 & 0 & 0 & -\widetilde{p_8} & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & -\widetilde{p_{14}} & -2 * \frac{\widetilde{p_{10}}}{3} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\frac{0.8}{p_1} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \widetilde{p_{12}} & -\widetilde{p_{11}} \end{bmatrix} \quad (6.18)$$

The characteristic polynomial was determined in Mathematica (See appendix) as:

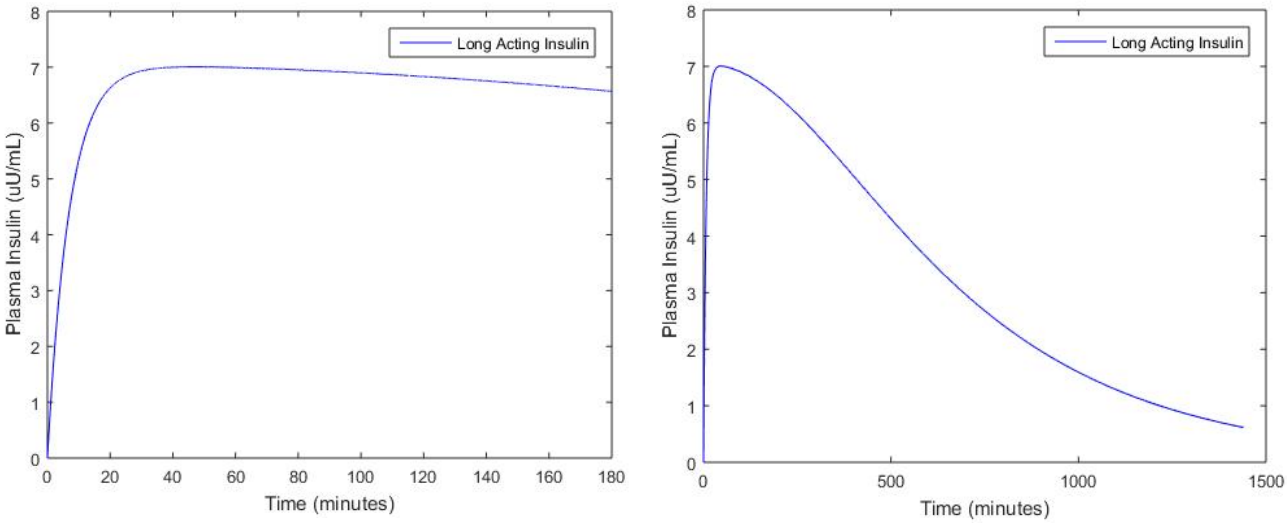
6.4. Model Simulations

This section will simulate the effects of the proposed term for insulin infusion on the minimal model as introduced in chapter 2 and the Glucagon Exercise Minimal Model proposed in chapter 5. The models are simulated in MATLAB, solved by ODE45 and the parameters are determined by LSQNONLIN.

6.4.1. Minimal Model and Insulin Infusion

By setting $t_{on} = 480$ (mins) and t_{deg}= 1200 (mins), a long acting insulin treatment is simulated, lasting for 24 hours.

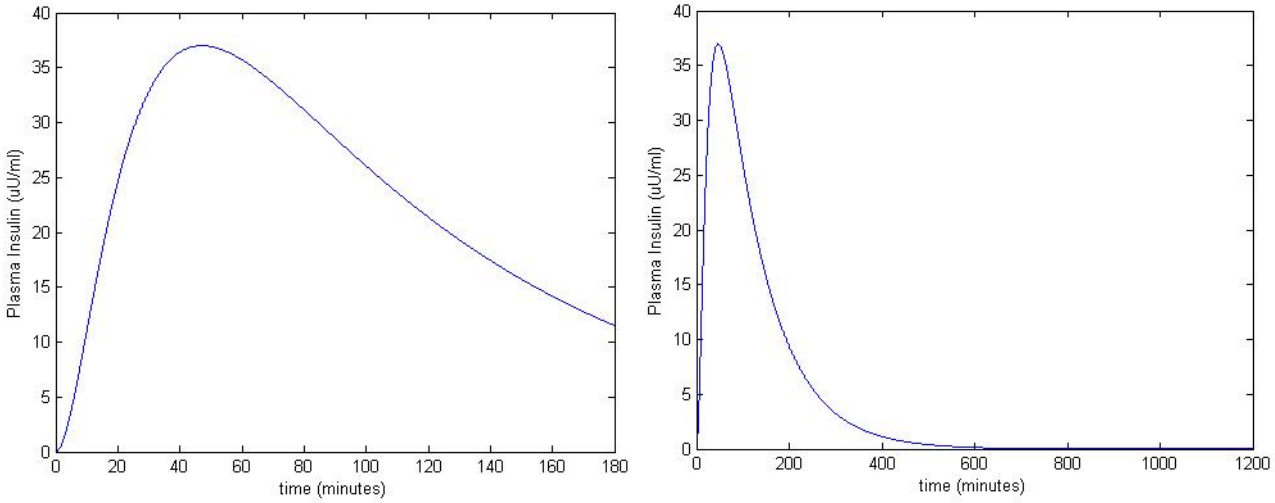
The minimal model was simulated, using the parameter values for the first four parameters as obtained by the glucagon minimal model, equations (3.4)-(3.7) in section 3.5.2, in figure 6.3, where α=10 and $t_{del} = 0$.



(a) (b)

Figure 6.3: I(t) for 180 minutes following a long acting insulin treatment (a) and I(t) for 24 hours following a long acting insulin treatment (b).

This can be adapted to simulated rapid acting insulin by changing the parameter values to give $t_{on} = 60$(mins) and t_{deg}= 300 (mins), e.g. Lispro or Aspart. Including this term into the minimal model gives the following responses from insulin in figure 6.4:



(a) (b)

Figure 6.4: I(t) for 180 minutes following a rapid acting insulin treatment (a) and I(t) for 24 hours following a long acting insulin treatment (b).

Note that the amount of units the simulated treatment increases the plasma insulin by is dependent on both the parameters α, in equation (6.5), and p_4, in equation (6.6). In physiological terms these will represent the strength of the insulin injection and the diffusion conditions in the subcutaneous tissue, discussed in section 6.1.

6.4.2. Exercise Glucagon Minimal Model and Insulin Infusion

As in chapter 5, the parameters u_3 and T_{dur} are fixed to adjust the model for various exercise intensities and durations respectively, replicating the protocols to the data obtained from various studies used to validate the models.

The datasets used to validate the models are obtained from Ahlborg et al. (1974), Wolfe et al. (1984), Ahlborg and Felig (1982) and Campbell et al. (2014). Despite three of the datasets having been obtained by healthy individuals, they will still be used to validate the model as insulin production from the beta cells will be replaced by exogenous insulin.

The parameter values will be presented at the end of this chapter in section 6.6 and can be found in appendix B.

6.5.2.1. Exercise at 30% of VO^{max}

The first simulation will be fitted to the dataset obtained by Ahlborg et al. (1974), whose method involved individuals exercising at 30% of their for 4 hours after a 12-14 hour fast. To represent individuals taking their basal insulin treatments before they went to bed the parameter controlling the time the treatment was taken will be set to t_{del}=780 minutes (13 hours). The results are shown in figures 6.4 and 6.5.

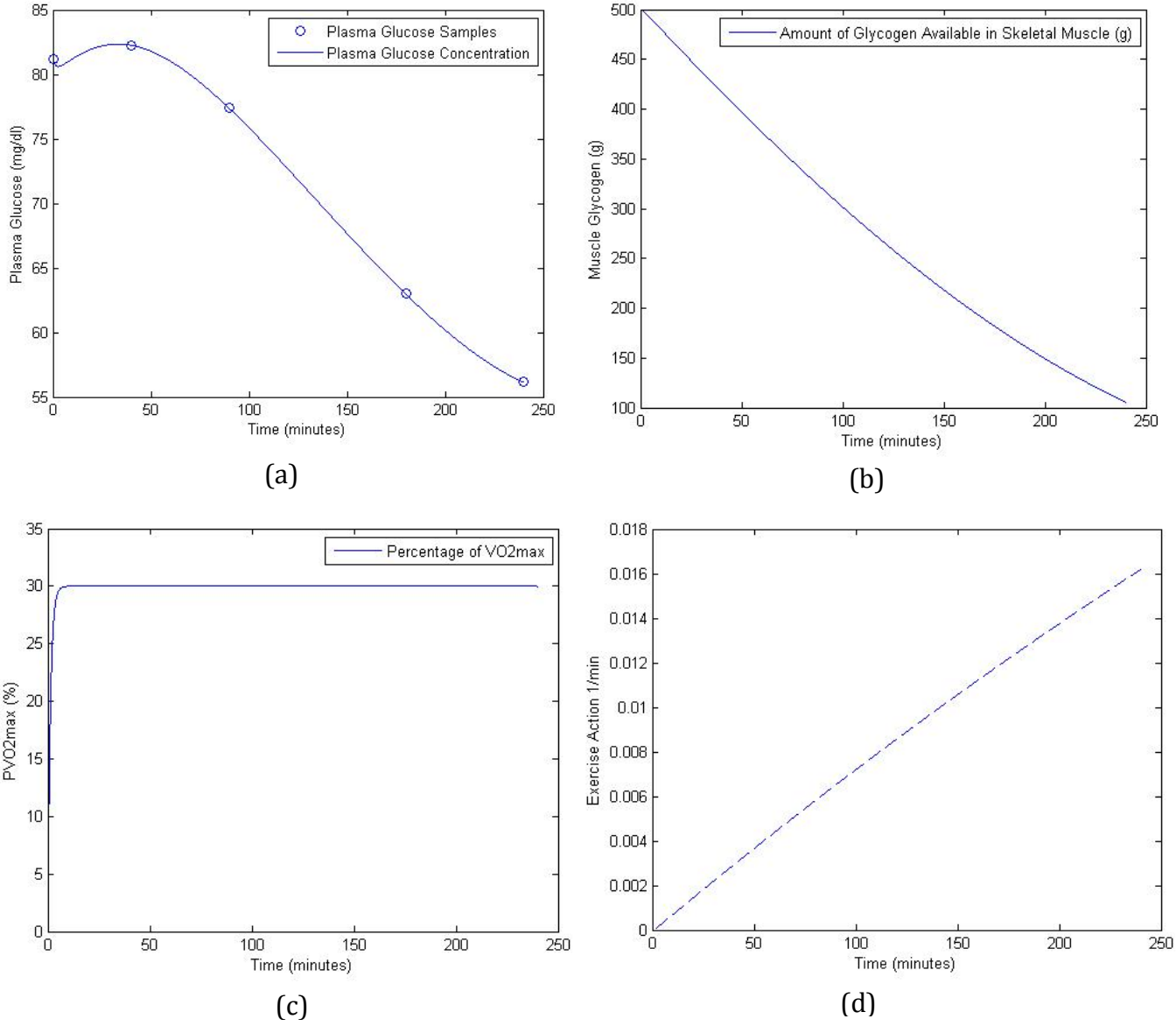


Figure 6.5: Exercise at 30% of VO_2^{max}: G(t) against plasma glucose measurements, (a), Gly(t), (b), PVO_2^{max} (t), (c) and A(t) (d).

The model equation for plasma glucose (a) provides an exact fit to the data set, predicting a slightly lower amount of muscle glycogen to be broken down than for the healthy patients, in addition to a slightly smaller amount of exercise activity.

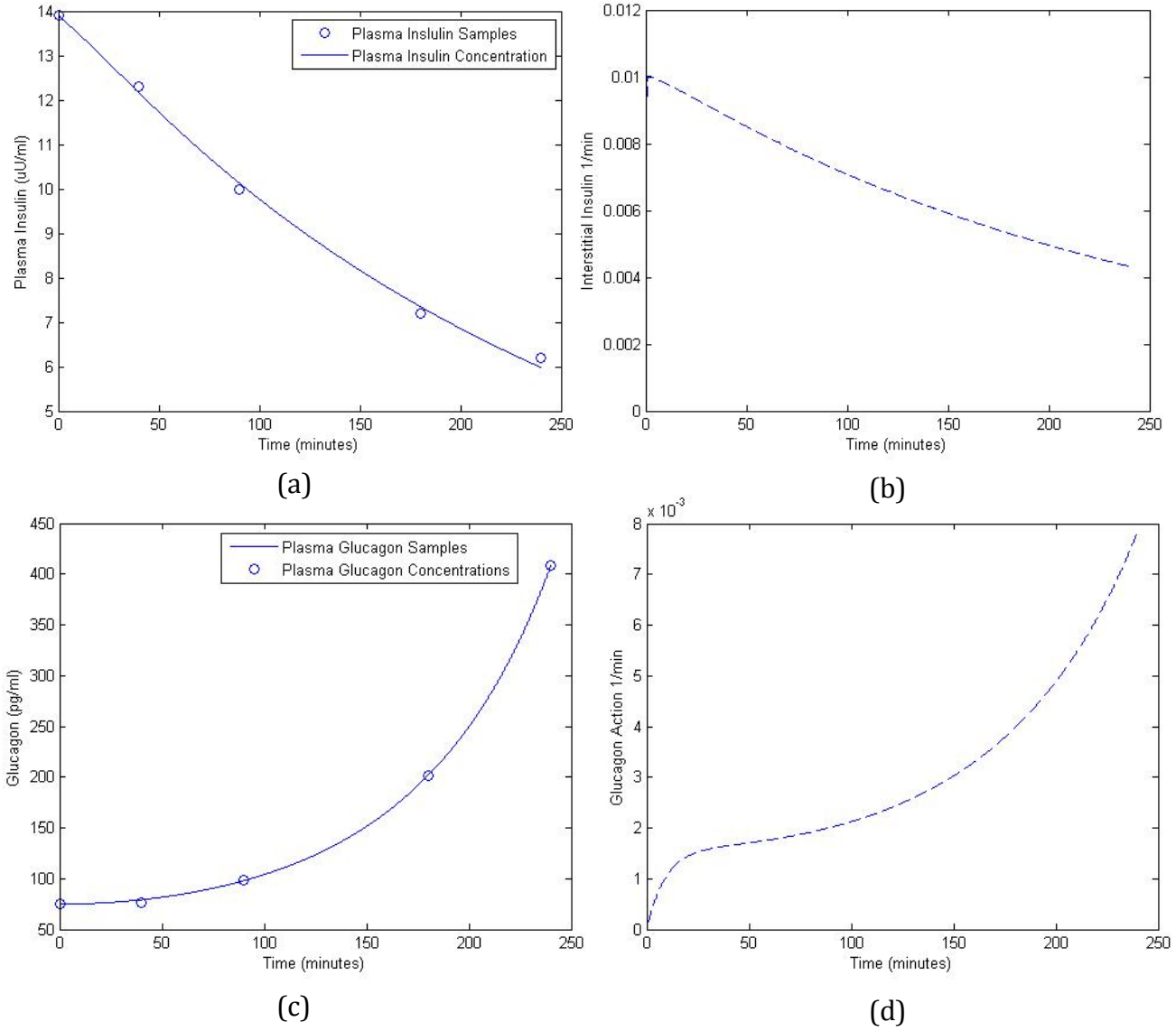


Figure 6.6: Exercise at 30% of VO_2^{max}: I(t) against plasma insulin measurements, (a), X(t), (b), E(t) against plasma glucagon measurements,(c) and Y(t) (d).

The equation for plasma insulin (a) provides a very close fit, which visually appears to have a better accuracy than for the healthy individual (figure 5.4.a). The model shows an excellent fit for plasma glucagon (c) to the data set, increasing fourfold accordingly. Both glucagon and interstitial insulin activity are of a lower magnitude than the simulation for healthy individuals as shown in figures 5.4.b and 5.4.d.

6.5.2.2. Exercise at 40% of VO^{max}

For the second simulation the model will be fitted to the dataset obtained by Wolfe et al. (1982), whose method involved individuals exercising at 40% of their VO^{max} for 1 hour following an overnight fast. To represent individuals taking their basal insulin treatments before they went to bed the parameter controlling the time the treatment was taken will be set to t_{del}=780 minutes (13 hours). The results are shown in figures 6.6 and 6.7.

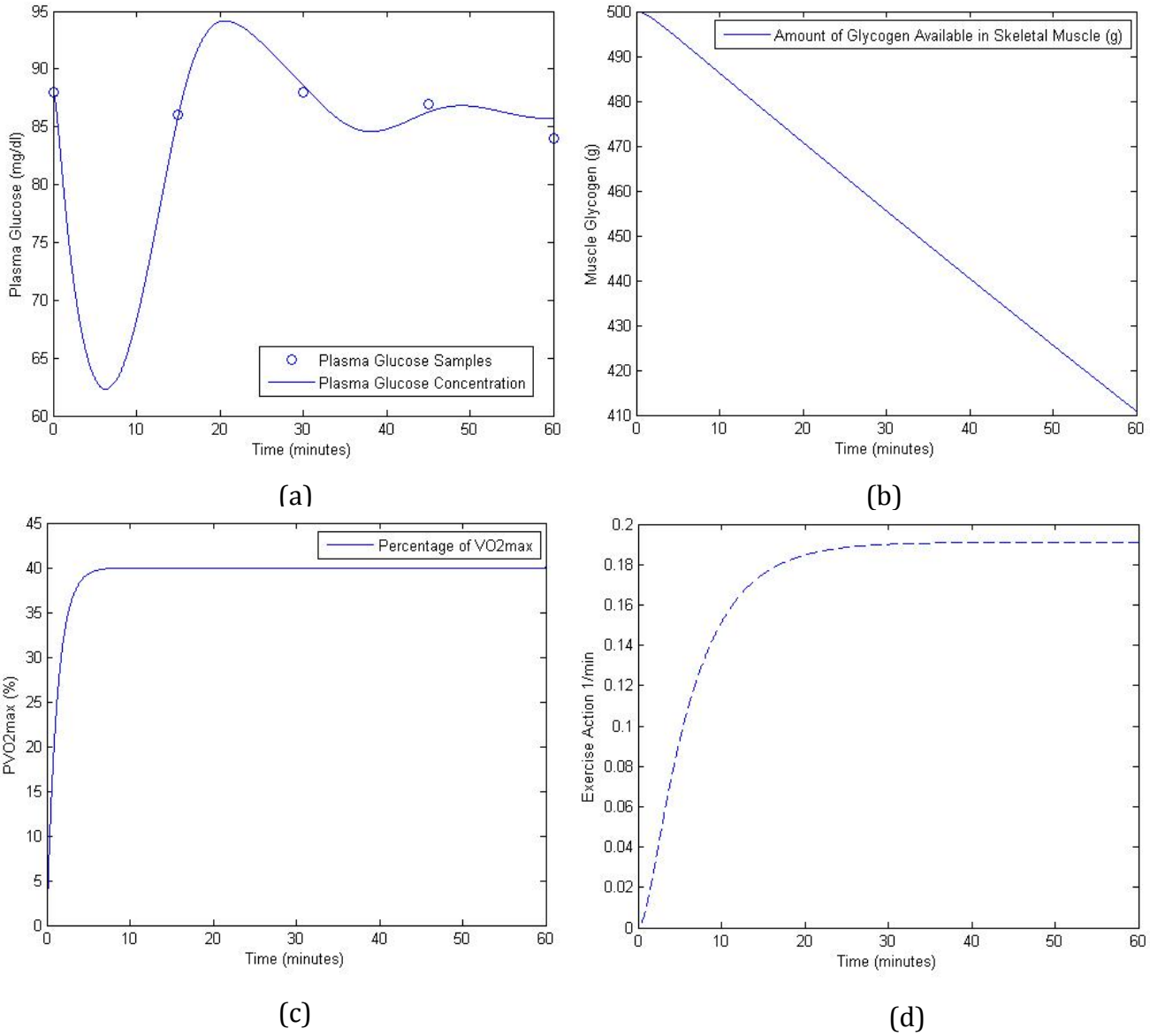


Figure 6.7: Exercise at 40% of VO_2^{max}: G(t) against plasma glucose measurements, (a), Gly(t), (b), PVO_2^{max} (t), (c) and A(t), (d).

Figure 6.7.a shows a good fit to the measurements for plasma glucose, however the fall predicted by G(t) appears exaggerated, as it is unlikely that such a dramatic fall in glucose levels would occur over such a short time period, especially given that the individuals is exercising at a fairly low intensity.

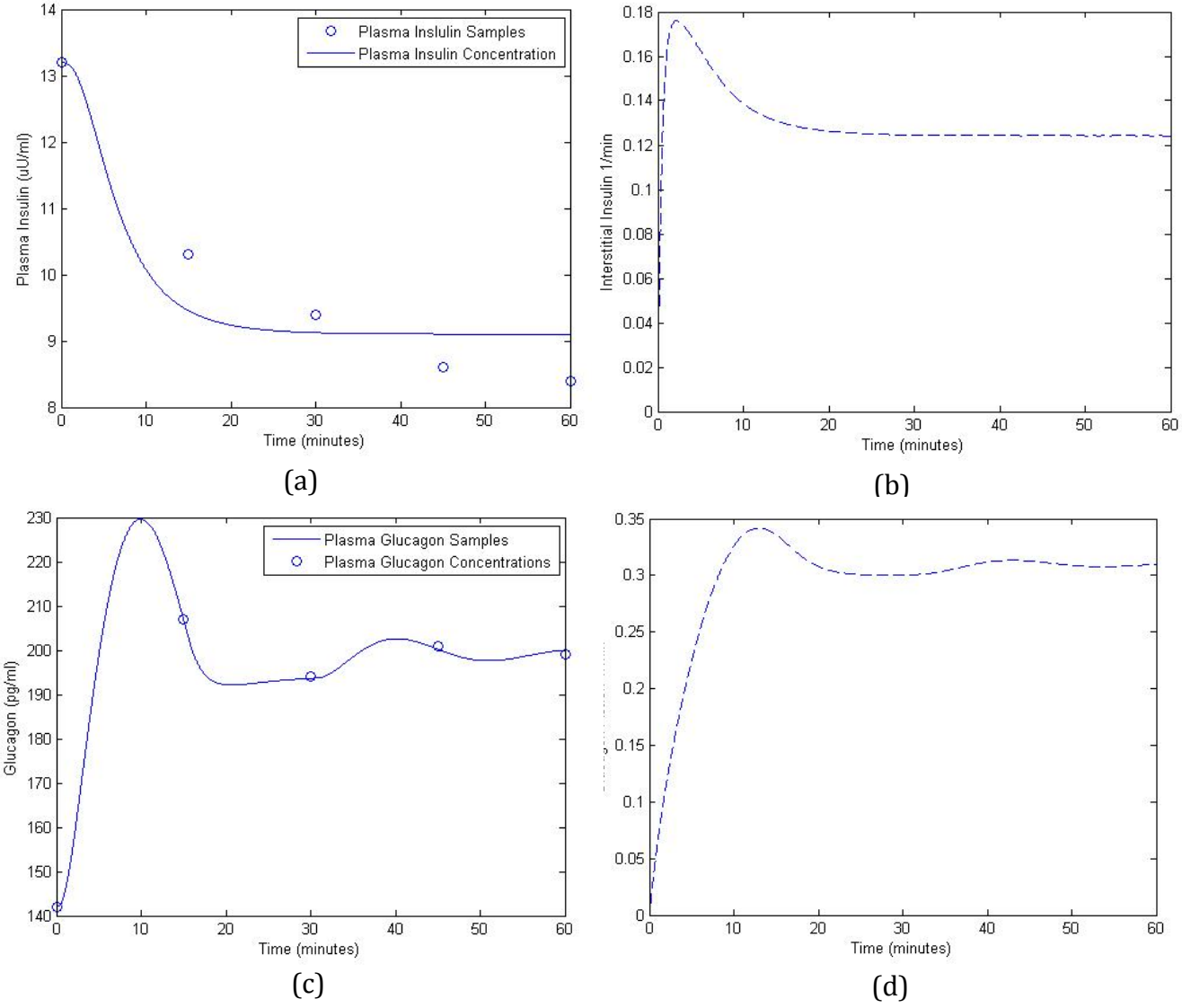


Figure 6.8: Exercise at 40% of VO_2^{max}: I(t) against plasma insulin measurements, (a), X(t), (b), E(t) against plasma glucagon measurements, (c) and Y(t), (d).

Figure 6.8 shows the capability of the model to accurately fit the data measurements for plasma glucagon; however it does a poor job at fitting the plasma insulin measurements. All simulations for this exercise protocol are almost identical as seen in figures 5.5 and 5.6 for the healthy individual, which validates the ability of the term for the exogenous insulin.

6.5.2.3. Exercise at 58% of VO^{max}

This simulation sets $u_3 = 58$ and $T_{dur} = 210$ to simulate the exercise protocol carried out in the studies by Ahlborg and Felig (1984). The participants began exercise following an overnight fast, therefore the initial measurements will be assumed to be the basal levels. It will also be assumed that individuals did not administer any rapid acting insulin, but did take their long acting insulin before they went to bed the previous evening. To represent individuals taking their basal insulin treatments before they went to bed the parameter controlling the time the treatment was taken will be set to t_{del}=780 minutes (13 hours). The results are shown in figures 6.6 and 6.7.

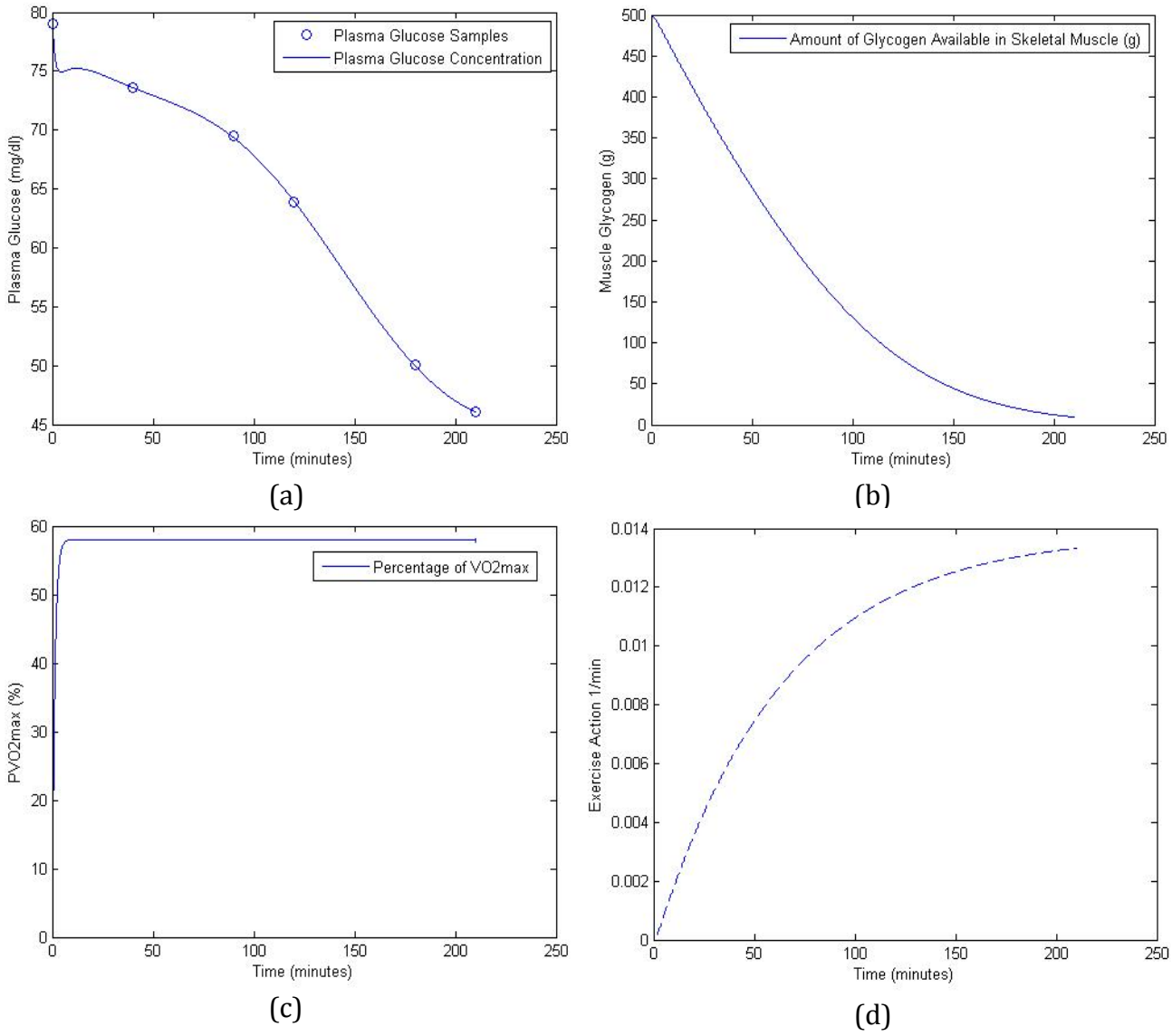


Figure 6.9: Exercise at 58% of VO_2^{max}: G(t) against plasma glucose measurements, (a), Gly(t), (b), PVO_2^{max} (t), (c) and A(t), (d).

The model provides an exact fit to the dataset for glucose (a) and shows complete depletion of glycogen levels. The model shows less exercise activity than in the previous simulation where $PVO_2^{max} = 40$, which is highly unlikely to be the case given that this protocol is at a higher exercise intensity and for a longer duration, i.e. the energy expenditure is significantly greater.

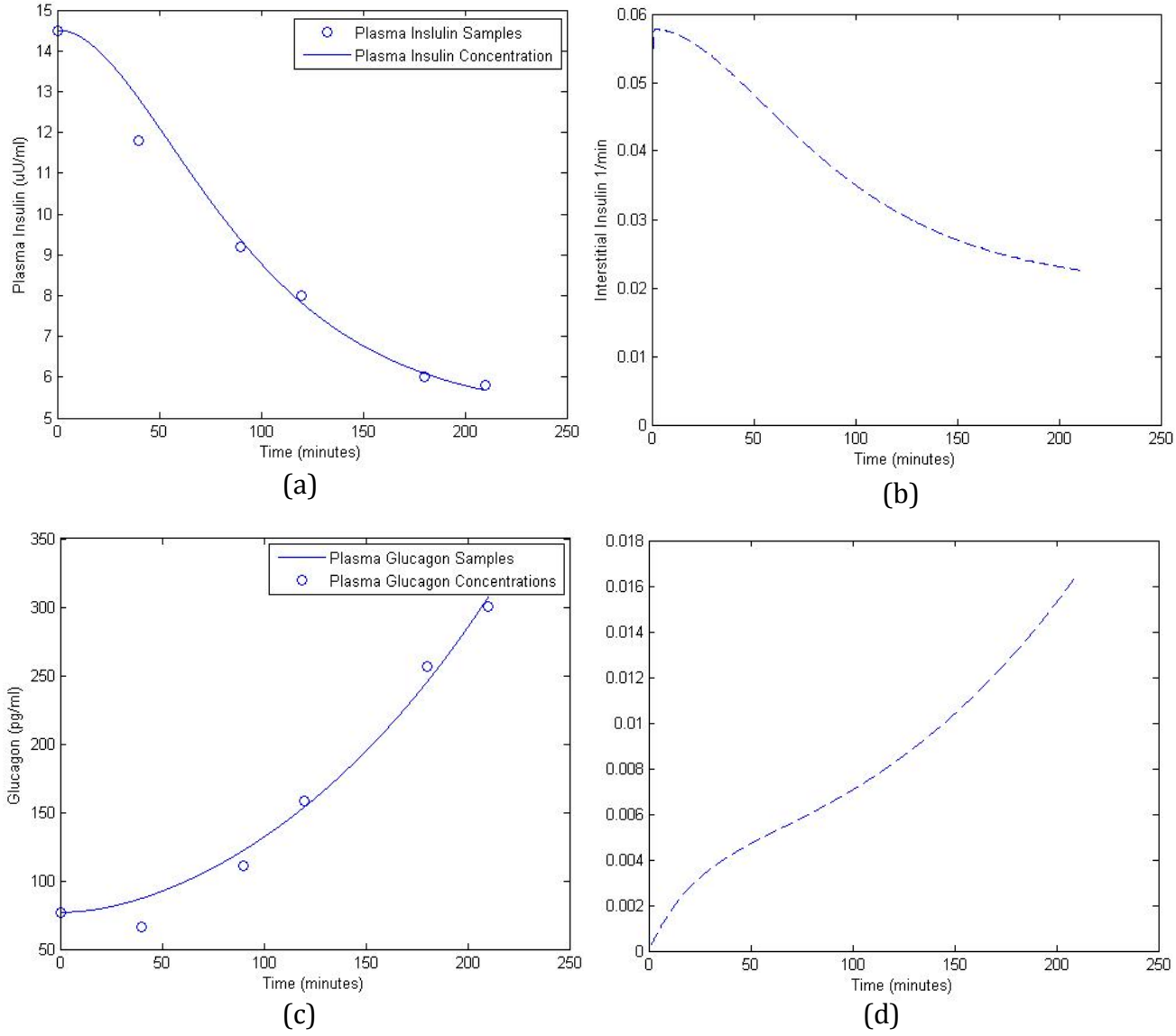


Figure 6.10: Exercise at 58% of VO_2^{max}: I(t) against plasma insulin measurements, (a), X(t), (b), E(t) against plasma glucagon measurements, (c) and Y(t), (d).

The model provides a fairly good fit to both plasma insulin (a) and plasma glucagon (c) measurements. The simulation for a type 1 diabetic patient predicts higher levels of glucagon activity and lower levels of interstitial insulin activity than is predicted for a healthy individual (figure 5.8).

6.5.2.4. Exercise at 70% of VO^{max}

The last simulation is fitted to a dataset obtained by Campbell et al. (2014) which consisted of type 1 diabetic individuals taking part in exercise at 70% of their VO^{max} for 45 minutes. Unlike the previous studies, these participants did not exercise following an overnight fast. Therefore this simulation will require both a long and rapid acting insulin treatment in order to accurately emulate the study carried out by Campbell and colleagues, as participants consumed a meal 1 hour beforehand. The long acting insulin was simulated by setting the parameters as t_{del1}=780 (mins) to represent the insulin administration taken 13 hours before starting exercise, the duration set to $t_{deg1} = 1200$ (mins) and the onset of the treatment as $t_{on1} = 480$ (mins). The rapid acting insulin was simulated by setting the time before the treatment was taken as t_{del2}=60 (mins), the duration of the treatment to be set as $t_{deg2} = 300$ (mins) and the onset as $t_{on1} = 60$ (mins). The parameters controlling the onset and clearance of the insulins are based on the characteristics as seen in table 6.1.

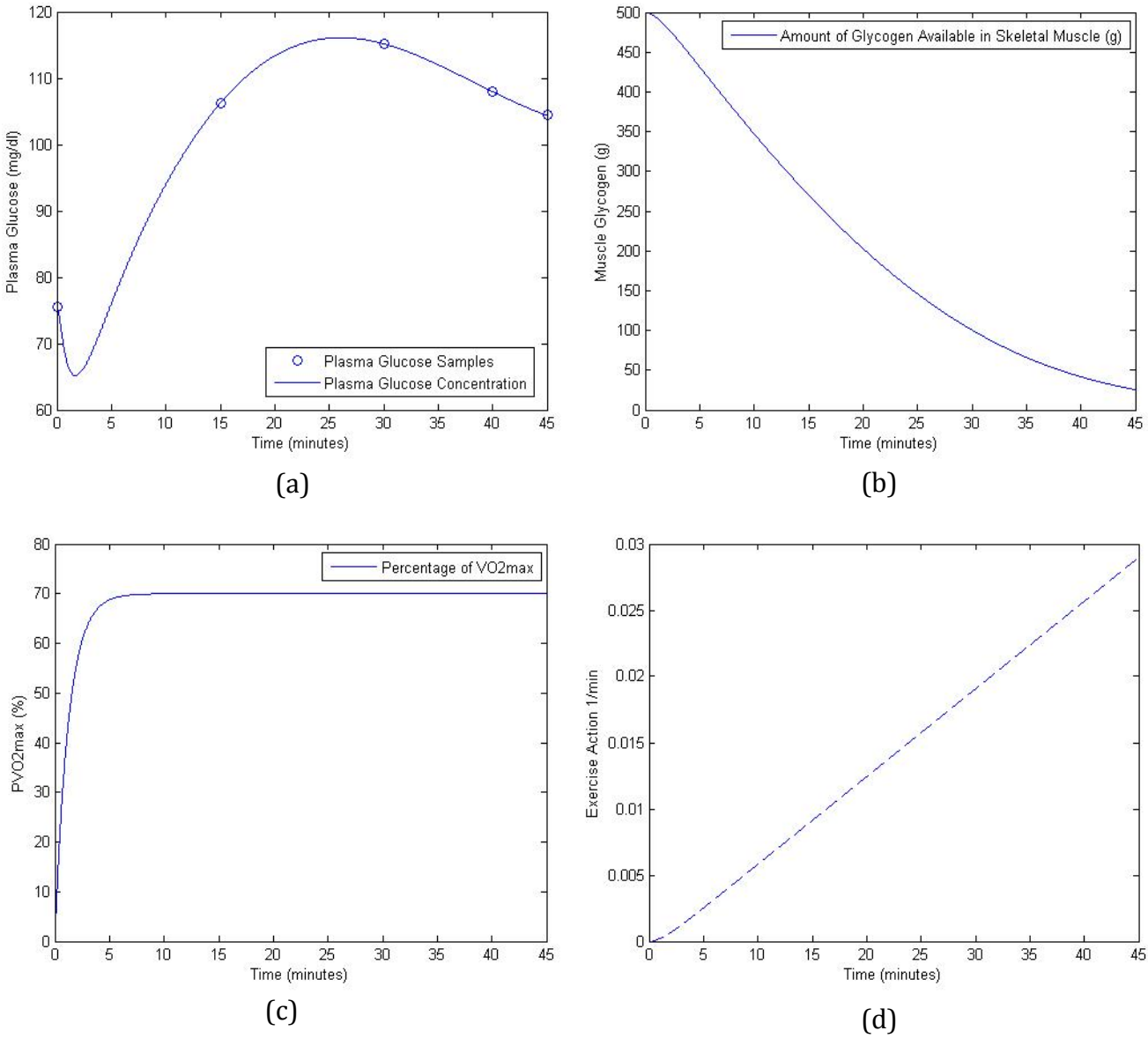
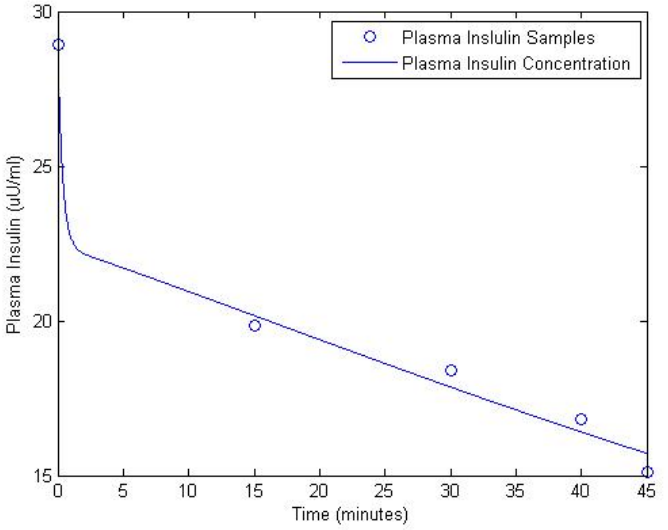
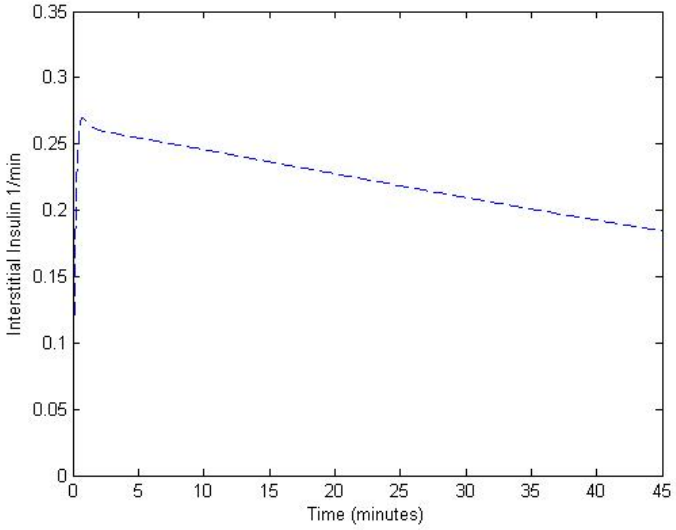


Figure 6.11: Exercise at 70% of VO_2^{max}: G(t) against plasma glucose measurements, (a), Gly(t), (b), PVO_2^{max} (t), (c) and A(t), (d).

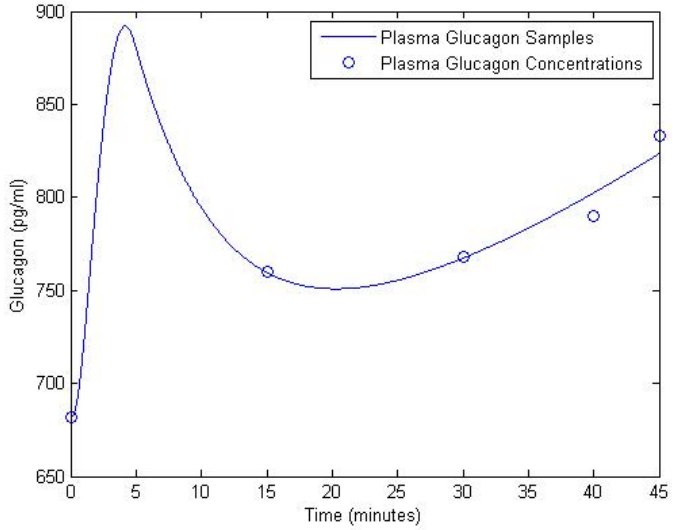
Figure 6.11.a shows an exact fit to the plasma glucose measurements by G(t), show an initial drop in levels followed by a rapid rise as the concentration of the counter-regulatory hormones in the plasma are increased in response to the increased utilisation of glucose. Figure 6.11.b show glycogen levels close to becoming entirely utilised towards the end of the exercise duration.



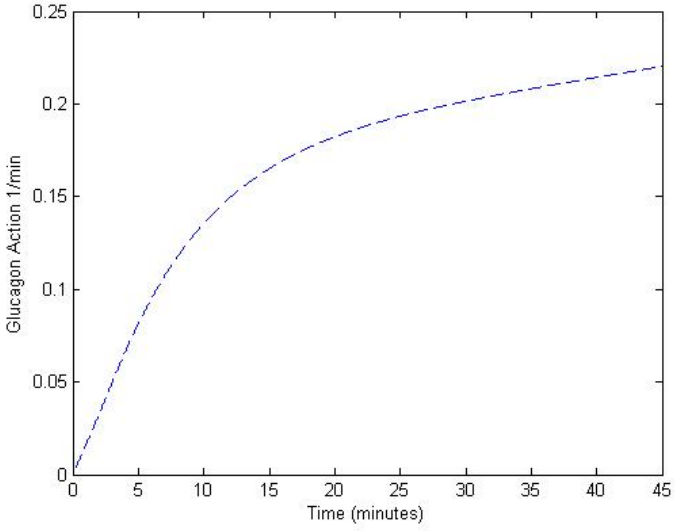
(a)



(b)



(c)



(d)

Figure 6.12: Exercise at 70% of VO_2^{max}: I(t) against plasma insulin measurements, (a), X(t), (b), E(t) against plasma glucagon measurements, (c) and Y(t), (d).

The fit of the model to the plasma insulin measurements (6.12.a) is still not ideal, however it is a much closer fit than the Glucagon Exercise Minimal Model was capable for a healthy patient as seen in figure 5.10.a.

Figure 6.12.d shows a fairly good fit for E(t) to the glucagon data, however the rapid increase in glucagon concentrations in the initial 5 minutes of exercise is rather excessive and, although it is quite likely that glucagon levels may overshoot the required level before smoothing out, the extent in which this model predicts is considered as unrealistic, although it is impossible to determine with sufficient data.

6.6. Discussion

The Glucagon Exercise Minimal Model adapted for a type 1 diabetic individual has been successfully fitted to all four data sets, with the simulations principally providing better fits to the datasets than the model for healthy individuals as implemented in chapter 5.

Table 6.3 is given below and shows the parameter values obtained by LSQNONLIN from the four simulations.

Table 6.3: Parameter values from the Glucagon Exercise Minimal Model adapted for type 1 diabetes.

Parameter	$\mathbf{PVO_2^{max}}$			
	30%	**40%**	**58%**	**70%**
$S_G = p_1$	0.01027182	$5.016009 * 10^{-7}$	0.018207975	0.13696906
p_2	4.78573664	2.175737907	4.84584071	4.31249661
p_3	0.00346643	0.029688922	0.01947456	0.05050953
p_4	0.06522939	0.424544428	0.00736092	2.78760207
p_5	6.73082717	$4.549747 * 10^{-9}$	$1.331945 * 10^{-12}$	82.16969825
p_6	0.10781389	0.349566126	0.04045856	0.08585775
p_7	$2.320701 * 10^{-6}$	$5.43164 * 10^{-4}$	$2.550857 * 10^{-6}$	0.00002443
p_8	0.00351130	0.710479808	0.00785531	0.13772318
p_9	$2.175208 * 10^{-9}$	1.38473137	$4.840995 * 10^{-8}$	9.13487573
p_{10}	0.10927957	0.05874696	0.12256887	0.39720033
p_{11}	0.00104748	0.18290123	0.01581215	$3.340849 * 10^{-14}$
p_{12}	$2.551955 * 10^{-6}$	$8.73518 * 10^{-4}$	$3.773498 * 10^{-6}$	$9.456928 * 10^{-6}$
p_{13}	0.39720317	0.3254266	0.93952685	1.01646595
$S_I = \frac{p_3}{p_2}$	$7.243263 * 10^{-4}$	0.01364545	0.00401882	106.53106953
$S_E = \frac{p_7}{p_6}$	$2.152606 * 10^{-5}$	0.001553823	$6.304863 * 10^{-5}$	0.01171236
$S_A = \frac{p_{12}}{p_2}$	0.00243627	0.0047759	$2.386455 * 10^{-4}$	2.83069598

There has been no difference noted between type 1 diabetic and healthy individuals in their abilities to respond to insulin, such that values for glucose effectiveness and insulin sensitivity are not expected to differ (Greenbaum et al., 2002). This conjecture is confirmed by the values for glucose effectiveness for all simulations in table 6.3 which are all within a close vicinity to the values returned by the model for healthy individuals (table 5.12).

The results for both insulin and glucagon sensitivity are surprising, in the sense that they are expected to increase with increasing energy expenditure and with the greatest amount of glycogen depletion (Colberg, 2008), (Kang et al. 1996). This would suggest that the simulations for $PVO_2^m = 58$ and $PVO^{max}{}_2 = 70$ ought to return the highest values for the parameters, which is true for the case where $PVO^{max} = 70$ but not for where $PVO^{max} = 58$, which returns significantly lower values than the simulation where $PVO^{max} = 40$. This may be due to varying individual factors, as it is known that insulin sensitivity is likely to be increased in both trained and younger individuals than for those who are sedentary and middle-aged or older (Henriksson, 1995).

Exercise sensitivity is also expected to increase with increased energy expenditure. For this to be the case, it would be anticipated that the simulation where $PVO^m = 58$ would return the highest value and where $PVO^{max} = 40$ to return the lowest. The results are slightly different from what was expected, however are still within the same magnitude of the foreseen results, suggesting the likelihood that this result was down to individual variability. This reinforces the need for an additional study consisting of the same individuals carrying out exercise at different intensities.

6.7. Summary

In this chapter the Glucagon Exercise Minimal Model was adapted to consider an individual with T1DM administering exogenous insulin.

The model provides an excellent fit to the plasma measurements obtained by Ahlborg et al. (1974) where $PVO^{\max} = 30$ and shows reasonable levels of insulin and glucagon activity in comparison to the IVGTT model. Exercise activity increases linearly with exercise intensity as a function of time, which is expected during low intensity exercise.

The fit against the data from Wolfe et al. (1984), where $PVO^{max} = 40$, is reasonable with the exception of plasma insulin. This is also the case for the model in chapter 5, where no diabetes was assumed; likely to be the result of insufficient data for the model to capture insulin dynamics.

This is also the case for the model in chapter 5 where no diabetes was assumed, therefore is likely to be caused by insufficient data for the model to capture insulin dynamics.

The simulations, where $PVO_2^{max} = 58$ and $PVO_2^{max} = 70$, although slightly under or overestimating the concentration of the hormones at certain points, overall provided better fits than the Glucagon Exercise Minimal Model for healthy individuals.

The majority of the key parameters are within reasonable magnitude of the acceptable ranges specified within the literature, with any marked differences likely to be the result of changes induced by physiological exercise.

As for the models in chapter 5, typically the ability of the model to fit the data improves as exercise intensity decreases, suggesting that either a bi-hormonal model is not sufficiently representative of higher intensity exercise or that there are still some mechanisms of glucose-insulin-glucagon dynamics that are not fully understood.

Overall, the term proposed for insulin administration has performed well in replacing β-cell secretion, and can be adapted accordingly to mimic the characteristics of various insulin treatments.

Chapter 7 Conclusions and Future Work

Incorporating regular exercise into the daily lives of individuals has been proven to have numerous health benefits, such as decreasing blood pressure, reducing the risk of heart disease as well as preventing obesity and the onset of many other health conditions. Whilst this is true for patients with diabetes; there is however, an additional factor to be considered when controlling glucose levels based on the evidence on the wide range of health benefits from regular exercise is growing for both type 1 (T1DM) and type 2 diabetics (T2DM). These include an increase in insulin sensitivity and glucose uptake; thus resulting in a decreased dependency on insulin treatments for patients with T1DM or severe T2DM, and the potential to reverse the onset of T2DM. The implications of these effects will not only lead to a reduction of the strain on health services but will allow for diabetic patients to have more freedom in leading a healthy and normal lifestyle.

Mathematical models for blood glucose regulation are considered as beneficial tools due to their ability to aid our understanding of system behaviours (Lakshmi Kiran et al., 2010), contribute towards the progression of artificial pancreas development (Herrero et al., 2013), have applications for automated insulin dosage adjustments (Lehnmann and Deutsch, 1992) and allow for the assessment of insulin sensitivity, glucose effectiveness (Vicini et al., 1997) and now glucagon sensitivity.

The primary goal of this thesis has been to develop a mathematical model showing the effects of exercise on blood glucose and its regulatory hormones. At present the majority of mathematical models for the glucose regulatory system consider glucose-insulin dynamics, in order to determine whether an individual has or is at risk of diabetes by measuring their ability to respond to or produce insulin. However, the counter-regulatory hormones become increasingly important during periods of low blood glucose, for example during prolonged physical activity.

The importance of glucagon in particular is increasingly becoming recognised. Understanding the contribution of glucagon to hepatic hyperglycaemia can help clinicians to identify the presence of diabetes, and which can then be treated by manipulating glucagon levels which has been proven to be beneficial to the diabetic state (Edgerton and Cherrington, 2011), (Siafarikas et al., 2012).

In chapter 3, three mathematical models were presented, each demonstrating glucose-insulin-glucagon dynamics during an Intravenous Glucose Tolerance Test (IVGTT). An IVGTT was chosen as the first scenario to model the effects of glucagon as there are many existing models that the model can be validated against and for the key parameter values such as insulin sensitivity, S_I, and glucose effectiveness, S_G, to be compared to. Despite glucagon's minor role, the models highlighted the importance of the action of glucagon to stimulate hepatic glucose production in order to counter the fall of glucose concentrations below the basal level, as often occurs as a result of the hypersecretion of insulin in response to an IVGTT. The results obtained from the three glucagon IVGTT models were compared and it was found that the linear model was by far inferior to the other two models. This result indicated that a model assuming a linear relationship between plasma glucose and insulin was insufficient during large fluctuations of the hormone, however there was not a significant difference between a nonlinear or a linear relationship between plasma glucose and glucagon, which is hypothesized to be due to the minimal role of glucagon during an IVGTT. Therefore, it is expected that the Linear Glucagon Minimal Model will to be inferior when modelling scenarios faced with low blood glucose, e.g. during exercise.

In chapter 5, the two models identified to be superior in chapter 3 were adapted to consider the physiologically mechanisms within the system that regulate glucose levels during exercise for a nondiabetic, healthy individual. Both models supported the hypothesis that glucose levels decline as glycogen stores are depleted and highlight the importance of the increase in the secretion of glucagon in order to prevent hypoglycaemia. The Glucagon Exercise Minimal Model was chosen as the optimal model for simulating the glucose regulatory system during exercise; it is capable of fitting physiological datasets, the performance of the simulations are in accordance with behaviour anticipated from literature and the physical implications of the key parameters are consistent. In addition, the parameters typically increased with increased energy expenditure, whereas the parameters of the Simplified Glucagon Exercise Minimal Model did not show any relationship between their values and exercise, and were often unreasonably high. Despite its drawbacks, the Simplified Glucagon Exercise Minimal Model did provide the better fit to the data for a number of simulations, as well as being advantageous in that it consisted of two quantities less than the Glucagon Exercise Minimal Model. This result suggests that linear

dynamics for glucagon are only suitable when glucagon activity is minimal. In addition, the Glucagon Exercise Minimal Model was able to return a parameter value for glucagon sensitivity. It is important to determine whether or not an individual, particularly a diabetic individual, has poor glucagon sensitivity as they will face an increased risk of hypoglycaemia, which, if left untreated, can result in severe health problems.

Chapter 6 adapted the equation for plasma insulin in the Glucagon Exercise Minimal Model to be representative of an individual with type 1 diabetes, i.e. the pancreas is incapable of producing insulin. From comparing the results of the two models (figures 5.4.a, 5.6.a, 5.8.a and 5.10.a to 6.6.a, 6.8.a, 6.10.a and 6.12.a) it was concluded that the model achieves a much better fit to the dataset for plasma insulin concentrations when it is simulated for a type 1 diabetic individual than when it is simulated for a nondiabetic, healthy individual. This result suggests that the terms proposed for insulin production are too simple for modelling the β-cell response to exercise.

From the observations within literature it was expected that insulin sensitivity would increase simultaneously with the amount of glycogen utilised for fuel during the activity (Colberg, 2008). Results from chapter 5 do not agree with this expectation, rather suggesting that insulin sensitivity increases with the rate of glycogen degradation, p_{10} (see tables 5.7-5.11); however without actual muscle glycogen data it is difficult to validate this conclusion.

The results of chapter 5 show that insulin sensitivity, glycogen mobilisation and glucose effectiveness increase with exercise intensity, which are all in agreement with the findings of Robergs et al. (1985), Adams (2013) and Hayashi et al. (2005). In comparison both glucagon and exercise sensitivity were at their highest when energy expenditure was at its greatest. This is to be expected for glucagon, given that the liver becomes more sensitised to the activity of glucagon with endurance exercise (Lavoie, 2005) and studies show that the glucagon response is typically greater the longer the exercise duration (Garrett and Kirkendall, 1999).

In chapter 6, the results for a type 1 diabetic individual slightly deviated from those for the healthy person in chapter 5. The model in chapter 6 showed the parameters for insulin sensitivity, glycogen mobilisation, glucose effectiveness, glucagon sensitivity and exercise sensitivity to all to be the highest the greatest exercise intensity. The parameter results in this chapter do not appear to show any particular

correlation between their values and exercise intensity or energy expenditure, however this is likely to be due to individual variations in fitness levels and diabetic states, again a consequence of insufficient data availability.

From the work of this thesis it can be determined that a combination of both endurance and high intensity exercise are beneficial for glucoregulatory health, whereas the results suggest that higher intensity exercise appears to be more beneficial for individuals with T1DM. This information is obtained from the results of the key parameters which offer an insight into glucoregulation, insulin sensitivity and glucose effectiveness. Before exercise recommendations can be adjusted these models require further validation to ensure the safety of participants and to gain a further insight into the duration and intensity of exercise most beneficial for improving the diabetic state.

In order to thoroughly validate the model, more data points are required. Validating a model with real life data is essential, as if it provides a bad fit it is unlikely that the model can provide good answers to the underlying questions under investigation (Guthrie et al., 2002). Due to the timescale and limitations of funding within this project, collecting data samples was not possible. It is strongly recommended that for a future project on this topic data ought to be obtained. Further, it is recommended that a study involving a number of participants with varying bodyweights and fitness levels who are required to take part in a number of exercise protocols of varying levels of intensity and durations is undertaken. It is suggested that a greater number of blood samples are taken than in the datasets presently available in order to improve the confidence intervals for the parameter fits.

The focus of this model is on exercise, therefore, since it is known that during exercise catecholamines are the main hormones whose concentrations markedly increase (Zouhal et al., 2008), future work ought to introduce the effects of these hormones on the glucose regulation system. Catecholamines are potent inhibitors of insulin release (Wilcox, 2005) therefore it is anticipated that introducing new variables to model the effects of the hormones may improve the accuracy of the model to capture the decline in plasma insulin.

An additional variable worth consideration would be the role of cortisol, which becomes particularly amplified in moderate-high intensity exercise (Hill et al., 2008). It is notable that the model typically provides better fits to the data from the lower

intensity exercise and therefore it may be that for higher intensities a bi-hormonal regulation model of glucose is insufficient and needs to take into account the effect of other counter-regulatory hormones.

The variable used to quantify exercise intensity in the models in this thesis was the percentage of VO_2^{max} taken from Roy and Parker (2007) (see chapter 5).
Using the percentage of VO_2^{max} to quantify exercise intensity assumes that oxygen consumption is linearly proportional to energy expenditure, which may not be true for all exercise, as was the case for the studies by Barstow and Mole (1991). It was hypothesised from these results that it would be possible that using PVO_2^{max} may not be a suitable for quantifying exercise intensity for individuals exercising at higher working rates. In the simulations from both chapters 5 and 6 the models provide much better fits to the datasets for the lower intensities. Therefore it is advised that further research on the relationship between energy expenditure and oxygen consumption should be completed in order to develop a more accurate equation.

Physiological concepts have been synthesised and implemented within a mathematical model that is capable of predicting blood glucose using a bi-hormonal approach during exercise, for both healthy and diabetic individuals. The results show that high intensity exercise is ideal for improving insulin sensitivity and glucose effectiveness, whereas exercise duration is the principal factor for improving the liver's sensitivity to glucagon. Evidence indicates that over a few years, following the diagnosis of type 1 diabetes the liver typically becomes desensitised to the action of glucagon, whereas type 2 diabetes is typically associated with poor insulin sensitivity. Therefore this project and studies of a similar nature could lead to new recommendations for managing both T1DM and T2DM.

Chapter 8 Thesis References

1. Ackerman, E., Gatewood, L. C., Rosevear, J. W. and Molnar, G. D. (1965) 'Model studies of blood-glucose regulation.' *The bulletin of mathematical biophysics,* vol. 27, no. 1, pp. 21-37.

2. Adams, O. P. (2013) 'The impact of brief high-intensity exercise on blood glucose levels' *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy,* vol. 6, pp. 113-122

3. Aguilera Gonzalez, A. and Darouach, M. (2015) 'Glucose-insulin system based on Minimal Model: A realistic approach' *2015 17th UKSIM-AMSS International Conference on Modelling and Simulation,* IEEE, pp. 55 -60.

4. Ahlborg, G., Felig, P., Hagenfeldt, L., Hendler, R. and Wahren, J. (1974) 'Substrate turnover during prolonged exercise in man' *The Journal of Clinical Investigation,* vol. 53, pp. 1080-1090.

5. Ahlborg, G. and Felig, P. (1982) 'Lactate and Glucose Exchange across the Forearm, Legs and Splanchnic Bed during and after Prolonged Leg Exercise' *The Journal of Clinical Investigation*, vol. 69, no. 1, pp.45-54.

6. Ajmera, I., Swat, M., Le Novere, N. And Chelliah, V. (2013) 'The impact of mathematical modelling on the understanding of diabetes and related complications' *CPT Pharmacometrics & Systems Pharmacology,* vol. 2, no. 2, pp. E54
7. American Diabetes Association (2004) 'Diagnosis and Classification of Diabetes Mellitus' *Diabetes Care,* vol. 27, no. 1, pp. S5-S10.
8. Amos, A. F., McCarty, D. J. and Zimmet, P. (1997) 'The rising global burden of diabetes and its complications: estimates and projections to the year 2010' *Diabetic Medicine,* vol. 14, no. 5., pp. S7-S85.
9. Andersen, K. E. and Højbjerre, M. (2005) 'A population-based Bayesian approach to the minimal model of glucose and insulin homeostasis.' *Statistics in Medicine,* vol. 15, no. 24, pp. 2381-2400.
10. Aronoff, S. L., Berkowitz, K., Shreiner, B. and Want, L. (2004) 'Glucose Metabolism and Regulation: Beyond Insulin and Glucagon' *Diabetes Spectrum,* vol. 17, no.3, pp. 183 -190.

11. Astrand, I. (1960) 'Aerobic work capacity in men and women with special reference to age' *Acta Physological Scandinavian Supplement,* vol. 49, no. 16, pp. 1-92.

12. Avogaro, A., Toffolo, G. and Cobelli, C. (1996) 'Epinephrine exerts opposite effects on peripheral glucose disposal and glucose-stimulated insulin secretion. A stable label intravenous glucose tolerance test minimal model study' *Diabetes, v*ol.45, pp. 1373-1378.

13. Bandyopadhyay, A. (2014) 'Validity of Cooper's 12 minute run test for estimation of maximum oxygen uptake in male university students.' *Biology of Sport,* vol. 32, no. 1, pp. 59-63.

14. Barstow, T. J. (1994) 'Characterization of VO2 kinetics during heavy exercise' *Medicine and Science in Sports and Exercise,* vol. 26, pp.1327-1334.

15. Basov, I., Meilunas, M. and Svitra, D. (1999) 'Glycemia monitoring: the problem of exogenous insulin input' *Mathematical Modelling and Analysis,* vol. 4, pp. 18-25

16. Berg, J. M., Tymoczko, J. L. and Stryer, L. (2002). Enzymes: Basic Concepts and Kinetics. In: Berg, J. M., Tymoczko, J. L. and Stryer, L. *Biochemistry, 5th edition*. 5th ed. New York: W.H.Freeman & Co Ltd.

17. Bergman, R. N., Ider, Y. Z., Bowden, C. R. and Cobelli, C. (1979) 'Quantitative estimation of insulin sensitivity.' *American Journal of Physiology,* vol. 236, no. 6, E667-E677.

18. Bergman, R. N, Phillips, L. S and Cobelli, C. (1981) 'Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose' Journal of Clinical Investigation*,* vol. 68, no. 6, pp. 1456-1467.

19. Bergman R. N. (1989) 'Toward physiological understanding of glucose tolerance. Minimal model approach.' *Diabetes,* vol. 38, no. 12, pp. 1512-1527.

20. Bergman, R. N., Finegood, D. T. and Khan, S. E. (2002) 'The evolution of β-cell dysfunction and insulin resistance in type 2 diabetes.' *European Journal of Clinical Investigation,* vol. 32, no. 3, pp. 35-45.

21. Blomstrand, E. and Saltin, B. (1999) 'Effect of muscle glycogen on glucose, lactate and amino acid metabolism during exercise and recovery in human subjects.' *The Journal of Physiology,* vol. 514, no. 1, pp. 293-302.

22. Bonjorn, V. M., Latour, M. G., Belanger, P. and Lavoie, J. M. (2002) 'Influence of prior exercise and liver glycogen content on the sensitivity of the liver to glucagon' *Journal of Applied Physiology,* vol. 92, no. 1, pp. 188-194.

23. Bolie, V. W. (1961) 'Coefficient of normal blood glucose regulation', *Journal of Applied Physiology,* vol. 16, no.5, pp. 738-788.

24. Borghouts, L. B. and Keizer, H. A. (2000) 'Exercise and insulin sensitivity: a review' *International Journal of Sports Medicine,* vol. 21, no. 1, pp. 1-12.

25. Brandt, M. (1999) *Rose-Hulman Institute of Technology.* Endocrine Notes Supplement; Chapter 5; Glucose Homeostasis. Available at: https://www.rose-hulman.edu/~brandt/Chem330/EndocrineNotes/Chapter_5_Glucose.pdf (Accessed on: 6th May 2016)

26. Buppajarntham, S. (2014). *Insulin.* Available at: http://emedicine.medscape.com/article/2089224-overview. (Accessed on: 11th April 2016).

27. Campbell, M., Walker, M., Trenell, M. I., Stevenson, E. J., Turner, D., Bracken, R. M., Shaw, J. A. and West, D. J. (2014) 'A Low–Glycemic Index Meal and Bedtime Snack Prevents Postprandial Hyperglycemia and Associated Rises in Inflammatory Markers, Providing Protection From Early but not Late Nocturnal Hypoglycemia Following Evening Exercise in Type 1 Diabetes.' *Diabetes Care,* vol. 37, no. 7, pp. 1845-54.

28. Cobelli, C., Federspil, G., Pacini, A., Salvan, A and Scandellari, C. (1982) 'An integrated mathematical model of the dynamics of blood glucose and its hormonal control' *Mathematical Biosciences,* vol. 58, no. 1, pp. 27-60.

29. Cobelli, C., Bettini, F., Caumo, A. and Quon, M. J. (1998) 'Overestimation of minimal model glucose effectiveness in presence of insulin response is due to undermodeling.' *American Journal of Physiology,* vol. 275, pp. E1031-E1036.

30. Coggan, A. R. (1991) 'Plasma glucose metabolism during exercise in humans.' *Sports Medicine,* vol. 11, no. 2, pp. 102-124.

31. Colberg, S. R. (2007) 'Physical activity, insulin action, and diabetes prevention and control.' *Current Diabetes Review,* vol. 3, no. 3, pp. 176-184.

32. Colberg, S. R. (2008) 'Increasing Insulin Sensitivity.' *Diabetes Self-Management,* Available at: http://www.diabetesselfmanagement.com/managing-diabetes/treatment-approaches/increasing-insulin-sensitivity/ (Accessed on 26th July 2016)

33. Colberg, S. R., Albright, A. L., Blissmer, B. J., Braun, b., Chasan-Taber, L., Fernhall, B., Regensteiner, J. G., Rubin, R. and Sigal, R. J. (2010) 'Exercise and Type 2 Diabetes' *Medicine in Sports Science and Exercise,* vol. 42, no. 12, pp. 2283-2303.

34. Cooper, D. M, Barsow, J., Bergner, A. and Paul Lee, W. (1989) 'Blood glucose turnover during high- and low-intensity exercise' *American Journal of Phsyiology,* vol, 257, no. 3, E405-E412

35. Costa-Junior, J. M., Ferreira, S. M., Protzek, A. O., Santos, G. J., Cappelli, A. P., Silveria, L. R., Zoppi, C., de Oliveria, C. A. M., Boschero, A. C., Carneiro, E. M. and Rezende, L. F. (2015) 'Endurance Training Inhibits Insulin Clearance and IDE Expression in Swiss Mice', *PloS one,* vol. 10, no. 3, p. e0118809.

36. Dalla Man, C., Caumo, A., Basu, R., Rizza, R., Toffolo, G. and Cobelli, C. (2004) 'Minimal model estimation of glucose absorption and insulin sensitivity from oral test: validation with a tracer method.' *American Journal of Physiology, Endocrionolgy & Metabolism,* vol. 287, no. 4, E637-E643.

37. Dalla Man, C., Rizza, R. A. and Cobelli, C. (2006) 'Mixed meal simulation model of glucose-insulin system.' *Annual International Conference of the IEEE Engineering in Medicine and Biology Society,* vol. 1,pp. 307-310.

38. Dalla man, C., Breton, M. D. and Cobelli, C. (2009) 'Physical Activity into the meal glucose-insulin model of type 1 diabetes: In silico studies' *Journal of Diabetes Science and Technol*ogy, vol. 3, no. 1, pp. 56 – 64.

39. Dalleck, L. and Dalleck, A., (2008) 'The ACSM exercise int4ensity guideline for cardiorespiratory fitness: why the misuse?' *Journal of Exercise Physiology online,* vol. 11, no. 4, pp. 1-11

40. De Gaetano, A. and Arino, O. (2000) 'Mathematical modleling of the intravenous glucose tolerance test. '*Journal of Mathematical Biology,* vol. 40, no. 2, pp. 136-168
41. De Pillis, L. (2005) 'Nondimensionalization.' Available at: https://www.math.hmc.edu/~depillis/PCMI2005WEBSITE/NonDimSlidesAndNotesWithAnswers.pdf (Accessed on : 23rd June 2016)
42. DeJesus, E. X. and Kaufman, C. (1987) 'Routh-Hurwitz criterion in the examination of eigenvalues ofd a system of nonlinear ordinary differential equations.' *Physical Review A,* vol 35, no. 12. 5288.
43. Del Prato, S., Marchetti, P. and Bonadonna, R. C. (2002) ' Phasic Insulin Release and Metabolic Regulation in Type 2 Diabetes' *Diabetes,* vol. 51, pp. S109-S116
44. Derouich, M. and Boutayeb, A. (2002) 'The effect of physical exercise on the dynamics of glucose and insulin' *Journal of Biomechanics,* vol. 35, pp. 911-917,
45. Diabetes.co.uk. (2012). 'When do you take your basal (long acting) Insulin?' Available at: http://www.diabetes.co.uk/forum/threads/when-do-you-take-your-basal-long-acting-insulin.34902/ (Accessed on: 22nd July 2016.)
46. Diabetes.co.uk. (2016). *Diabetes Prevalence.* Available at: http://www.diabetes.co.uk/diabetes-prevalence.html. (Accessed on: 30th March 2016).
47. DiPietro, L., Dzoira, J., Yeckel, C. W. and Neufer, P. D. (2006) 'Exercise and improved insulin sensitivity in older women; evidence of the enduring benefits of higher intensity training.' *Journal of Applied Physiology, vol. 100, no. 1, pp. 142-140*.
48. Donner, T. (2015) 'Insulin – Pharmacology, Therapeutic Regimens and Principles of Intensive Insulin Therapy.' In: De Groot LJ, Chrousos G, Dungan K, et al., editors. Endotext [Online]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available at: http://www.ncbi.nlm.nih.gov/books/NBK278938/ (Accessed on: 16th August 2016.)
49. Edgerton, D. S. and Cherringotn, A. D. (2011) 'Glucagon as a Critical Factor in the Pathology of Diabetes.' *Diabetes,* vol. 60, no. 2, pp. 377-380.
50. Fernandez, M., Villasana, M. and Streja, D. (2009) 'The Minimal Model of Glucose Disappearance in Type 1 Diabetes.' *Biomedical Data and Applications,* vol. 224, pp. 295-315.

51. Fischer, H. P. (2008) 'Mathematical modelling of complex biological systems: from parts lists to understanding systems behaviour.' *Alcohol Research and Health,* vol. 31, no. 1, pp. 49-59.

52. Fitches, M. J. (2015) *'Mathematical Modelling of Diabetes* ', BSc Dissertation, Oxford Brookes University.

53. Flynn, G. (2003) 'Enzyme Kinetics.' *C2407: Chemistry*, Available at: http://www.columbia.edu/itc/chemistry/chem-c2407/hw/ (Accessed on: 3rd August 2016.)

54. Galbo, H., Holst, J. J. and Christensen, N. J. (1975) 'Glucagon and plasma catecholamine response to graded and prolonged exercise in man' *Journal of Applied Physiology,* vol. 37, no. 1, pp. 70-77.

55. Garrett, W. E. and. Kirkendall, D. T (1999). *Exercise and Sport Science*. Philadelphia, Pennsylvania, United States: Lippincott Williams and Wilkins.

56. Gatineau, M., Hancock, C., Holman, N., Outhwaite, H., Oldridge, L., Christie, A. and Ells, L. (2014). *Adult obesity and type 2 diabetes.* Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/338934/Adult_obesity_and_type_2_diabetes_.pdf (Accessed on: 30th March 2016).

57. Giles, G. (2016). 'High and Low Blood Sugar - Managing The Ups and Downs*.'* Available at: https://www.verywell.com/managing-high-and-low-blood-sugar-3289565 (Accessed on: 30th July 2016).

58. Godoy-Matos, A. F. (2014) 'The role of glucagon on type 2 diabetes at a glance.' *Diabetology & Metabolic Syndrome,* vol. 6, no. 1, pp 1.

59. Goldman, L. and Schafer, A. L. (2012). *Goldman's Cecil Medicine: Expert Consult Premium Edition.* 24th ed. Philadelphia: Elsevier Saunders. pp. 1355.

60. Goodwin, M. L. (2010) 'Blood glucose regulation during prolonged, submaximal, continuous exercise: A guide for clinicians.' *Journal of Diabetes in Science and Technology,* vol. 4, no. 35, pp. 694-795.

61. Goodyear, L. K. and Kahn, B. B. (1998) 'Exercise, glucose transport and insulin sensitivity' *Annual Review of Medicine,* vol. 49, pp. 235-261.

62. Greenbaum. C. J., Prigeon, R. L. and DAlessio, D., A. (2002) 'Impaired beta-cell function, incretin effect, and glucagon suppression in patients with type 1 diabetes who have normal fasting glucose.' *Medscape,* Available at:

http://www.medscape.com/viewarticle/432407_4 (Accessed on: 5th August 2016.)

63. Gupta, S. K. (2012) 'The relevance of confidence interval and P-value in inferential statistics.' *Indian Journal of Pharmacology,* vol. 44, no. 1, pp. 143-144.
64. Guthrie, W., Filliben, J. and Heckert, J. (2002). Process Modelling. In: Croarkin, C. and Tobias, P. *Engineering Statistics Handbook*. Available at: http://www.itl.nist.gov/div898/handbook/pmd/section4/pmd44.htm (Accessed on: 8th August 2016).
65. Hargreaves, M. and Spriet, L. (2006). *Exercise Metabolism*. 2nd ed. Champaign: Human Kinetics. Pp. 68-70.
66. Hayashi, T., Wojtaszewski, J. F., Goodyear, L. J. (1997) 'Exercise regulation of glucose transport in skeletal muscle' *American Journal of Physiology,* vol. 263, no. 6, pp. E1039-E1051.
67. Hayashi, Y., Nagasaka, S., Takahashi, N., Kusaka, I., Ishibashi, S., Numao, S., Lee, D. J., Taki, Y. Ogata, H., Tokuyama, K. and Tanaka, K. (2005) 'A single about of exercise at higher intensity enhances glucose effectiveness in sedentary men.' *Journal of Clinical Endocrinology Metabolism,* vol. 90, no. 7, pp. 4035-4040.
68. Henquin. J. C., Ishiyama, N., Nenquin, M., Ravier, M. A. and Jonas, J. C. (2002) 'Signals and Pools Underlying Biphasic Insulin Secretion.' *Diabetes,* vol. 51, no. 1, S60-S67.
69. Henriksson, J. (1995) 'Influence of Exercise on Insulin Sensitivity.' *European Journal of Preventive Cardiology,* vol. 2, no. 4, pp. 303-309.
70. Herrero, P., Georgiou, P., Oliver, N., Reddy, M., Johnston, D. and Toumazou, C. (2013) 'A composite model of glucago0glucose dynamics for in-silico testing of bihormonal glucose controllers' *Journal of Diabetes Science and Technology*, vol. 7, no. 4, pp. 941-951.
71. Hill, E. E., Zack, E., Battaglini, C., Viru, M., Viru, A. and Hackney, A. C. (2008) 'Exercise and circulating cortisol levels: the intensity threshold effect.' *Journal of Endocrinological Investigation,* vol. 31, no. 2, pp. 587-591.
72. Hildebrandt, P. (1991) 'Subcutaneous absorption ofn insulin in insulin-dependent diabetic patients. Influence of species, physicochemical properties

of insulin and physiological factors', *Danish Medical Bulletin,* vol. 38, no. 4, pp. 337-346

73. Holloszy, J. O. (2005) 'Exercise-induced increase in muscle insulin sensitivity' *Journal of Applied Physiology,* vol. 99, no. 1, pp. 338-343.

74. Huang, M., Guo, H. And Xinyu, S. (2012) 'Modeling Impulsive Injections of Insulin: Towards Artificial Pancreas' *SIAM Journal of Applied Mathematics,* vol. 72, no. 5, pp.1524-2548

75. Insulin Sensitivity. (2016). *Diabetes.co.uk,* Available at: http://www.diabetes.co.uk/insulin/insulin-sensitivity.html (Accessed on: 14th July 2016).

76. Jensen, J., Rustad, P. I., Kolnes, A. J., Lai, Y. C. (2011) 'The role of skeletal muscle glycog breakdown for regulation of insulin sensitivity by exercise' *Frontiers in Physiology,* vol. 2, pp. 112

77. Jeukendrup, A. and Gleeson, M. (2010). *Sport Nutrition*. 2nd ed. Champaign: Human Kinetics. p67.

78. Kang, J., Robertson, R. J., Hagberg, J. M., Kelley, D. E., Goss, F. L., Dasilva, S. G., Suminski, R. R. and Utter, A. C. (1996) 'Effects of Exercise Intensity on Glucose and Insulin Metabolism in Obese Individuals and Obese NIDDM Patients.' *Diabetes Care,* vol. 19, no. 4, pp. 341-349.

79. Katz, A., Broberg, S., Sahlin, K. and Wahren, J. (1986) 'Leg glucose uptake during maximal dynamic exercise in humans' *American Journal of Physiology and Metabolism,* vol. 251, no. 1, pp. E65-E70

80. Khardori, R, (2013) 'Changing paradigms in type 2 diabetes mellitus.' *Indian Journal of Endocrinology and Metabolism,* vol. 17, no. 1, S68-S71.

81. Kjaer, M. (1998) 'Hepatic glucose production during exercise' *Advances in Experimental Medicine and Biology,* vol. 441, pp 171-179.

82. Krucki, G. (2014) 'Age of onset for type 2 diabetes: know your risk.' *Healthline,* Available at: http://www.healthline.com/health/type-2-diabetes-age-of-onset#Overview1 (Accessed on: 15th August 2016.)

83. Lakshmi Kiran, K., Kandpal, M. and Lakshminarayanan, S. (2010) 'Characterization of frequently sampled intravenous glucose tolerance test using scaling and sensitivity analysis of MINMOD.' *The 2010 Intervnational Conference on Modelling, Identification and Control (ICMIC),* PP. 179-184

84. Latif, Z. A. (2007). 'More benefit in the treatment of diabetes from modern insulin.' Available at: http://www.thedailystar.net/news-detail-9179 (Accessed on: 22nd July 2016).

85. LaValle, S. M. (2006) *Planning Algorithms.* [ebook] University of Cambridge Press. 1st Edition. Available at: http://planning.cs.uiuc.edu/(Accessed on: 16th August 2016.)

86. Lavioe, C. (2005) 'Glucagon receptors: effect of exercise and fasting', *Canadian Journal of Applied Physiology,* vol. 30, no. 3, pp. 313-327.

87. Lavoie, C., Ducros, F., Bourque, J., Langelier, H. and Chiassion, J. L. (1997) 'Glucose metabolism during exercise in man :the role of insulin and glucagon in the regulation of hepatic glucose production and gluconeogenesis' *Canadian Journal of Physiology and Pharmacology,* vol. 75, no. 1, pp. 26-35.

88. Lehmann, E. D. and Deutsch, T. (1992) 'A physiological model of glucose-insulin interaction in type 1 diabetes mellitus' *Journal of Biomedical Engineering,* vol. 14, no. 3, pp. 235-245

89. Lehmann, E. D., Tarin, C., Bondia, J., Teufel, E. and Deutsch, T. (2007) 'Incorporating a Generic Model of Subcutaneous Insulin Absorption into the AIDA v4 Diabetes Simulator: 1. A Prospective Collaborative Development Plan', *Journal of Diabetes Science and Technology,* vol. 1, no. 3, pp. 423-435.

90. Li, J. and Kuang, Y. (2001) 'Analysis of IVGTT Glucose-Insulin interaction models with time delay' *Discrete and continous dynamical systems – series B,* vol. 1, no. 1, February 2001, pp. 103-124.

91. Liu, W. And Tang, F. (2008) 'Modeling a simplified regulatory system of blood glucose at molecular levels' *Journal of Theoretical Biology,* vol. 252, no. 4, pp. 608-620.

92. Luyckx, A. S., Pirnay, F. and Lefebvre, P. J. (1978) 'Effect of glucose on plasma glucagon and free fatty acids during prolong exercise' *European Journal of Applied Physiology* and Occupational Therapy, vol. 39, no. 1, pp. 53-61.

93. Lyapunov Stability (2015). 'Engineering Progam', *FRTN05,* Available atL http://www.control.lth.se/media/Education/EngineeringProgram/FRTN05/2015/ (Accessed on: 1st August 2016).

94. MacLaren, D. and Morton, J. (2012). Principles of metabolic regulation. In: *Biochemistry for sport and exercise metabolism*. Chichester: John Wiley & Sons, Ltd. p129-144.

95. Magdelaine, N., Chaillous, L., Guilhem, I., Poirier, J, Krempf, M., Moog, C. and Le Carpentier, E. (2015) 'A long term model of glucose-insulin dynamics of type 1 diabetes' *IEEE transactions on biomedical engineering,* vol. 62, no. 6, pp1546-1552.

96. Magombedze, G., Nduru, P., Bhunu, C. P. and Mushayabasa, S. (2009) 'Mathematical modelling of immune regulation of type 1 diabetes.' *Biosystems,* vol. 102, no. 2, pp. 88-98.

97. Makroglou, A., Li, J. and Kuang, Y. (2006) 'Mathematical models and software tools for the glucose-insulin regulatory system and diabetes: an overview' *Applied Numerical Mathematics* ,vol. 26, no. 3, pp. 559-572

98. Marliss, E. B. And Vranic, M. (2002) 'Intense exercise has unique effects on both insulin release and its role in glucoregulation' *Diabetes,* vol. 51, no. 1, pp. S271-S283

99. Marmarelis, V. and Mitsis, G. (2014). *Data-driven Modeling for Diabetes*. Heidelberg: Springer-Verlag, pp. 40.

100. McCrimmon, R. and Sherwin, R. S. (2010) 'Hypoglycemia in Type 1 Diabetes.' *Diabetes,* vol. 59, no. 1, pp. 2333-2339.

101. McCulloch, D. K., Nathan, D. M. and Mulder, J. E. (2016). *Patient information: Diabetes mellitus type 1: Insulin treatment (Beyond the Basics).* Available: http://www.uptodate.com/contents/diabetes-mellitus-type-1-insulin-treatment-beyond-the-basics. (Accessed 16th June 2016.)

102. McDonald, C., Dunaif, A. and Finegood, D. T. 'Minimal-Model Estimates of Insulin Sensitivity Are Insensitive to Errors in Glucose Effectiveness' *J Clin Endocrinol Metab,* vol. 85, no. 7, pp. 2504-2508

103. The Medical Biochemistry Page (2016) *Gluconeogenesis: Endogenous Glucose Synthesis,* Available at: http://themedicalbiochemistrypage.org/gluconeogenesis.php *(*Accessed on: 24th May 2016).

104. Meinke, M. H. and Edstrom, R. D. (1990) 'Muscle Glycogenolysis; regulation of the cyclic interconversion of phosphorylase a and phosphorylase b' *The Journal of Biological Chemistry,* vol. 266, no. 4, pp. 2259-2266.

105. Merry, T., L. and McConell, G., K. (2009) 'Skeletal muscle glucose uptake during exercise: a focus on reactive oxygen species and nitric oxide signalling.' *IUBMB Life,* vol. 61, no. 5, pp. 479-484.

106. Miller, C. D., Phillips, L. S., Ziemer, D. C., Gallina, D. L., Cook, C. B., and El-Kebbi, I. M. (2001) 'Hypoglycemia in Pateints with Type 2 Diabetes Mellitus.' *Archives of Internal Medicine,* vol. 161, no. 13, pp. 1653-1659.

107. Moore, P. (2011) 'How to calculate your energy expenditure.' *Triathlete Europe,* Available at: http://triathlete-europe.competitor.com/2011/05/18/how-to-calculate-your-energy-expenditure (Accessed on: 4th August 2016).

108. Moore, M. C., Coate, K. C., Winnick, J. J., An, Z. and Cherrington, A. D. (2012) 'Regulation of Hepatic Glucose Uptake and Storage in Vivo.' *Advanced Nutrition,* vol. 3, pp. 286-294.

109. Munkhammar, J. (no date) 'Integrating Factor.' From *MathWorld*--A Wolfram Web Resource, created by Eric W. Weisstein. Available at: http://mathworld.wolfram.com/IntegratingFactor.html (Accessed on 14th June 2016).

110. Muniyappa, R., Lee, S., Chen, H. and Quon, M. J. (2008) 'Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations and appropriate usage.' *American Journal of Endocrinology & Metabolism,* vol. 294, no. 1, E15-26.

111. Natalucci, S., Ruggeri, P., Cogo, C. E., Picchio, V. and Burattini, R. (2000) 'Insulin sensitivity and glucose effectiveness estimated by the minimal model technique in spontaneously hypertensive and normal rats.' *Experimental Physiology,* vol. 85, no. 6, pp. 775-781.

112. Nishida, Y., Higaki, Y., Fujimi, K., Kiyonaga, A., Shindo, M., Sato, Y. and Tanaka, H. (2001) 'Effect of Mild Exercise Training on Glucose Effectiveness in Healthy Men.' *Diabetes Care,* vol. 24, no. 5, pp. 1008-1013.

113. Nittala, A., Ghosh, S., Stefanovski, D., Bergman, R. and Wang, X. (2006) 'Dimensional analysis of MINMOD leads to definition of the disposition index of glucose regulation and improved simulation algorithm' *Biomedical Engineering OnLine, Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1560383/pdf/1475-925X-5-44.pdf (*Accessed on: 21st April 2016).

114. Pacini, G. and Bergman, R. N. (1986) 'MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently samples intravenous glucose tolerance test' *Computer Methods and Programs in Biomedicine,* vol. 23, no. 2, pp. 113-122

115. Petersen, K. F., Price, T. B. and Bergeron, R. (2004) 'Regulation of net hepatic glycogenolysis and gluconeogenesis during exercise: impact of type 1 diabetes' *Journal of Clinical Endocrinology & Metabolism,* vol. 29, no. 9, pp 4656-4664

116. Plowman, S. A. and Smith, D. L. (2010) 'Exercise Physiology for Health, Fitness and Performance' *Lippincott Williams and Wilkins,* vol. 3.

117. Quon, M. J., Cochran, C., Taylor, S. I. and Eastman, R. C. (1994) 'Non-insulin-mediate glucose disappearance in subjects with IDDM. Discordance between experimental results and minimal model analysis.' *Diabetes,* vol. 43, no. 7, pp. 890-896.

118. Reaven, G. M. (1988) 'Banting lecture 1988. Role of insulin resistance in human disease.' *Diabetes,* vol. 37, no. 12, pp. 1595-1607.

119. Richter, E.A., Ruderman, N. B., Haralambos, G., Belur, E. R. and Galbo, H. (1982) 'Muscle glycogenolysis during exercise: dual control by epinephrine and contractions.' *American Journal of Physiology, Endocrinology and Metabolism,* vol. 242, no. 1, pp. E25-E32

120. Richter, E. A., Ploug, T. and Galbo, H. (1985) 'Increased muscle glucose uptake after exercise. No need for insulin during exercise' *Diabetes,* vol. 34, no. 1, pp. 1041-1048

121. Robergs, R. A, Pearson, D. R., Costill, D. L., Fink, W. K., Pascoe, D. D., Benedict, M. A., Lambert, C. P. and Zachweija, J. J. (1985) 'Muscle glycogenolysis during differing intensities of weight-resistance exercise.' *Journal of Applied Physiology,* vol. 70, no. 4, pp. 1700-1706.

122. Ross, R. (2003) 'Does Exercise without Weight Loss Improve Insulin Sensitivity?' *Diabetes Care,* vol. 26, no. 3, pp. 944-945.

123. Roy, A. And Parker, R. S (2007) 'Dynamic Modeling of Exercise Effects on Plasma Glucose and Insulin Levels' *Journal of Diabetes Science and Technology.* Vol 1, no.3, pp. 338-347.

124. Sakamoto, M., Higaki, Y., Nishida, Y., Kiyonaga, A., Shindo, M., Tokuyama, K. and Tanaka, H., (1999) 'Influence of mild exercise at the lactate threshold on glucose effectiveness.' *Journal of Applied Physiology,* vol. 87, no. 6, pp. 2305-2310

125. Schovanec, L. and Gilliam, D. (1999) 'ODE Chapter 4: Stability', *Math 5540-5332,* Available at: http://texas.math.ttu.edu/~gilliam/ttu/ode_pde_pdf/Ch4.pdf (Accessed on: 12th May 2016)

126. Seals, D. R., Hagberg, J. M., Hurley, B. F., Ehsani, A. A. and Holloszy, J. O. (1984) 'Effects of endurance training on glucose tolerance and plasma lipid levels in older men and women.' The Journal of the American Medical Association, vol. 252, no. 5, pp. 645-649.

127. Siafarikas, A., Johnston, R. J., Bulsara, M. K., O'Leary, P., Jones, T. W. and Davis, E. A. (2012) 'Early Loss of the Glucagon Response to Hypoglycemia in Adolescents With Type 1 Diabetes.' *Diabetes Care,* vol. 35, no. 8, pp. 1757-1762.

128. Sorensen, J. T. (1985) 'A physiological model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes.' PhD. University of California.

129. Sternlicht, E., Barnard, R. J. and Grimditch, G. K. (1989) Exercise and insulin stimulate skeletal muscle glucose transport through different mechanisms.' *American Journal of Physiology,* vol. 256, no. 2, E227-230.

130. Stumvoll, M., Goldstein, B. J. and van Haeften, T. W. (2005) 'Type 2 diabetes: principles of pathogenesis and therapy.' *The Lancet,* vol. 365, no. 9467, pp. 1333-1346.

131. Sullivan, L. (2012). *Confidence Interval.* Available at: http://sphweb.bumc.bu.edu/otlt/MPH-Modules/BS/BS704_Confidence_Intervals/BS704_Confidence_Intervals2.html. (Accessed on: 21st June 2016).

132. Sulston, K. W., Ireland, W. P. and Praught, J. C. (2006) 'Hormonal Effects on Glucose Regulation' *Journal of Mathematics,* vol. 1, no. 1.

133. D. Svitra, 'Dynamics of Physiological System', *Mokslas*, Vilnius, 1989 (in Russian)

134. Svitra, D., Basov, R. and Vilktye, R. (2010) 'Modelling of glycaemia dynamics: impact of physical exercises.' *Nonlinear Analysis: Modelling and Control,* vol. 15, no. 2, pp. 213-232.

135. Taguchi, N., Aizawa, T., Sato, Y., Ishihara, F. and Hashizume, K. (1995) 'Mechanism of glucose-induced biphasic insulin release: physiological role of adenosine triphosphate-sensitive K+ channel-independent glucose action.' *Endocrinology,* vol. 136, no. 9, pp. 3942-3948.

136. Teixeira, R. E. and Mailin, S. (2008) 'The next generation of artificial pancreas control algorithms' *Journal of Diabetes Science and Technology,* vol. 2, pp.105-112

137. Thomaseth, K., Brehm, A., Pavan, A., Pacini, G. and Roden, M. (2014) 'Modeling glucose and free fatty acid kinetics during insulin-modified intravenous glucose tolerance test in healthy humans: role of counter-regulatory response'. *American Journal of Physiology – Regulatory, Integrative and Comparative Physiology,* vol. 307, no. 3, pp. R321-331.

138. Todd, A. J. (2008) 'Inclusion of a glycogen regulation mathematical model into a contextual metabolic framework', PhD, University of North Carolina

139. Tonelli, J., Kishore, P., Lee, D. E. and Hawkins, M. (2005) 'The regulation of glucose effectiveness: how glucose modulates its own production.' *Current Opinion in Clinical Nutrition and Metabolic Care,* vol. 8, no. 4, pp. 450-456.

140. Tornoe, C. W., Jacobsen, J. L., Pedersen, O., Hansen, T. and Madsen, H. (2004) 'Grey-box modelling of pharmacokinetic/pharmacodynamics systems.' *J Pharmacokinet Pharmacodyn.* Vol 31, no. 5, pp. 401-17.

141. Valletta, J. J., Chipperfield, A. J., Clough, G. F. And Byrne, C. D. (2014) 'Daily energy expenditure, cardiorespiratory fitness and glycaemic control in people with type 1 diabetes', PLoS one, vol 9, no. 5, e97534.

142. Van Groesen, E. and Molenaar, J. (2007). Dimensional Analysis and Scaling. In: Haberman, R. *continuum modeling in the physical sciences*. Philadelphia: Society for Industrial and Applied Mathematics, SIAM. pp. 7-30.

143. Van Hasssel, R. (2006) 'Lipschitz condition and Lipschitz continuity.' *G1156,* Available at: http://www.win.tue.nl/~rvhassel/Onderwijs/Old-Onderwijs/2WA23-2011/HO-03.pdf (Accessed on: 16th August 2016.)

144. Verkerke, A., Paran, C., Atkinsn, J. and Funai, K. (2015) 'Increased energy expenditure and insulin sensitivity, but not protection from obesity, in phosphatidylethanolamine methyltransferase knockout mice on long-term high-fat diet feeding.' The FASEB Journal, vol. 29, no. 1, S824.6.

145. Vicini, P., Caumo, A. and Cobelli, C. (1997) 'The hot IVGTT two-compartment minimal model: indexes of glucose effectiveness and insulin sensitivity.' *American Journal of Physiology,* vol. 273, no. 5, E1024-E1032.

146. Vranic, M., Kawamore, R., Pek, S., Kovacevic, N. And Wrenshall, G. A. (1976) 'The essentiality of insulin and the role of glucagon in regulation glucose utilization and production during strenuous exercise in dogs' *Journal of Clinical Investigation,* vol. 57, no. 2, pp. 245-155

147. Wahren, J., Felig, P., Ahlborg, G. and Jorfeldt, L. (1971) 'Glucose metabolism during leg exercise in man' *The Journal of Clinical Investigation,* vol. 50, no. 12, pp. 2715-2725

148. Wasserman, D. H. and Cherrington, A. D. (1991) 'Hepatic fuel metabolism during muscular work: role and regulation' *American Journal of*

Physiology, vol 260, pp. E811-24.

149. Wilcox, G. (2005) 'Insulin and Insulin Resistance.' *Clinical Biochemical Review,* vol. 26, no. 2, pp. 19-39.

150. Wolfe, R. R., Wolfe, M. H., Nadel, E. R. and Shaw, J. H. (1984) 'Isotopic determination of amino acid-urea interactions in exercise and humans' *Journal of Applied Physiology,* vol. 56, no. 1, pp. 221-229

151. World Health Organisation. (2016). '*Diabetes'.* Available at: http://www.who.int/mediacentre/factsheets/fs312/en/ (Accessed on: 11th April 2016.)

152. Worthington Biochemical Corporation. (2016). '*Introduction to Enzymes.'* Available at: http://www.worthington-biochem.com/introbiochem/substrateConc.html (Accessed on: 27th July 2016).

153. Wuang, M., Li, J., Lim, G. E. and Johnson, J. D. (2013) 'Is dynamic autocrine insulin signalling possible? A mathematical model predicts picomolar concentrations of extracellular monomeric insulin within human pancreatic islets', *PloS one,* vol. 8, no. 6, E4860.

154. Yates, T. L. and Fletcher, L. R. (2000) 'Prediction of a glucose appearance function from foods using deconvolution.' *IMA Journal of Mathematics Applied in Medicine and Biology,* vol. 17, no. 2, pp. 169-184.

155. Zill, D. G. (2013). *A First Course in Differential Equations with Modeling Applications.* 10th ed. Boston: Brooks/Cole. 37.

156. Zouhal, H., Jacob, C., Delamarche, P. and Gratas-Delamarche, A. (2008) 'Catecholamines and the effects of exercise, training and gender.' *Sports Medicine,* vol. 38, no. 5, pp. 401-423.

Appendix A

Datasets

Blood measurents from Pacini and Bergman (1984) from a healthy, non-diabetic individual during and IVGTT.

Time	Glucose (mg/dl)	Insulin (μU/ml)
0	92	11
2	350	26
4	287	130
6	251	85
8	240	51
10	216	49
12	211	45
14	205	41
16	196	35
19	192	30
22	172	30
27	163	27
32	142	30
42	124	22
52	105	15
62	92	15
72	84	11
82	77	10
92	82	8
102	81	11
122	82	7
142	82	8
162	85	8
182	90	7

Blood measurements taken by Ahlborg et al. (1974) from healthy, non-diabetic individuals exercising at 30% of their in the post-absorptive state for 240 minutes.

Time	Glucose (mg/dl)	Insulin (µU/ml)	Glucagon (pg/ml)
0	81.2	13.9	75
40	84.6	12.3	76
90	77.4	10	99
180	63	7.2	201
240	56.2	6.2	408

Blood measurements taken by Wolfe et al. (1984) from healthy, non-diabetic individuals exercising at 40% of their in the post-absorptive state for 60 minutes

Time	Glucose (mg/dl)	Insulin (µU/ml)	Glucagon (pg/ml)
0	88	13.2	142
15	86	10.3	207
30	88	9.4	194
45	87	8.6	201
52	86	8.7	194
60	84	8.4	199

Blood measurements taken by Ahlborg and Felig (1982) from healthy, non-diabetic individuals exercising at 58% of their in the post-absorptive state for 210 minutes

Time	Glucose (mg/dl)	Insulin (µU/ml)	Glucagon (pg/ml)
0	4.39	14.5	77
40	4.09	11.8	66
90	3.86	9.2	111
120	3.55	8	158
180	2.78	6	257
210	2.56		

Appendix B Parameter Values

B.1. Linear Glucagon Model

Parameter	Value	Unit
$S_G = p_1$	0.02717445	min^{-1}
p_2	0.11739499	$min^{-1}(mg/dl)$
p_3	0.02085256	$min^{-1}(mg/dl)$
p_4	0.07243666	min^{-1}
p_5	0.37843489	$min^{-2}\,(\mu U/ml)$
p_6	0.00237924	min^{-1}
p_7	0.00800919	$min^{-2}\,(pg/ml)$
G_0	289.00705341	mg/dl
I_0	393.16692531	$\mu U/ml$

B.2. Glucagon Minimal Model

B.2.1. Dimensional Model

Parameter	Value	Unit
$S_G = p_1$	0.02059000	min^{-1}
p_2	0.02219000	min^{-1}
p_3	$1.37999 * 10^{-5}$	$min^{-2}\,(\mu U/ml)^{-1}$
p_4	0.32000001	min^{-1}
p_5	0.00367636	$min^{-2}\,(\mu U/mL)$
p_6	0.14200001	min^{-1}
p_7	$2.17999 * 10^{-4}$	$min^{-2}\,(pg/ml)^{-1}$
p_8	0.04940002	min^{-1}
p_9	$1.78999 * 10^{-5}$	$min^{-2}\,(pg/ml)$
S_I	$6.21902 * 10^{-4}$	$min^{-1}(\mu U/ml)^{-1}$
S_E	0.00153521	$min^{-1}(pg/ml)^{-1}$
G_0	293	mg/dl
I_0	360	$\mu U/ml$

B.2.2. Dimensionless Model

Parameter	Dimensional Value	Non-Dimensional value rescaled by $\tau = \frac{1}{p_1}$	Non-Dimensional value rescaled by $\tau = \frac{1}{p_4}$	Non-Dimensional value rescaled by $\tau = \frac{1}{p_8}$
$S_G = p_1$	0.02058	0.01756659	0.00941376	0.00941386
p_2	0.02218	0.11408124	0.03733535	0.037336576
p_3	0.0000137	0.0000360401	0.0000201577	0.0000201556
p_4	0.32	0.03563689	0.2783405	0.278343671
p_5	0.0032	0.00630156	0.00334216	0.003342215
p_6	0.142	1.1440989	0.7025258	0.702525919
p_7	0.000217	0.06857451	0.00796508	0.007964075
p_8	0.0494	0.04687327	0.499999	0.5
p_9	0.0000178	0.001533393	0.000024545	0.00001
S_I	0.000617	0.000315916	0.000539908	0.00053928
S_E	0.001528	0.0599379	0.01539908	0.0113
G_0	293	292	279	279
I_0	360	366	360	360

B.3. Linear Glucagon Minimal Model

B.3.1. Dimensional Model

Parameter	Value	Unit
$S_G = p_1$	0.02808122	min^{-1}
p_2	0.00996122	min^{-1}
p_3	$7.31888 * 10^{-6}$	$min^{-2}\,(\mu U/ml)^{-1}$
p_4	0.27943170	min^{-1}
p_5	0.00290469	$min^{-2}\,(\mu U/mL)$
p_6	0.19225742	min^{-1}
p_7	0.00364470	$min^{-2}\,(pg/ml)$
p_8	0.01530144	$(mg/dl)min^{-1}$
S_I	$7.34737 * 10^{-4}$	$min^{-1}(\mu U/ml)^{-1}$
G_0	293	mg/dl
I_0	360	$\mu U/ml$

B.3.2. Dimensionless Model

Parameter	Dimensional Value	Non-Dimensional value rescaled by $\tau = \frac{1}{p_1}$	Non-Dimensional value rescaled by $\tau = \frac{1}{p_4}$	Non-Dimensional value rescaled by $\tau = \frac{1}{p_6}$
$S_G = p_1$	0.010682729	0.01997831	0.0153103	0.0150861
p_2	0.039225779	0.0144932	0.0231139	0.02259839
p_3	0.000020016	0.0000108854	0.00001459	0.000014613
p_4	0.296424834	0.20202604	0.22646731	0.212060508
p_5	0.003663205	0.00197596	0.0023889	0.002129929
p_6	0.097285237	0.485124233	0.1222461	0.221008791
p_7	0.000724184	0.002605806	0.00124715	0.00152487
p_8	0.000724178	0.037376378	0.0116759	0.01809859
S_I	0.000510277	0.000751068	0.00063153	0.000646669
G_0	293	282	279	282
I_0	360	411	406	410

B.4. Glucagon Exercise Minimal Model and Simplified Glucagon Exercise Minimal Model

B.4.1. 30% of VO^{max}

Parameter GEMM	GEMM	Parameter	SGEMM
$S_G = p_1$	0.017553609	p_1	0.00150000
p_2	2.239076769	p_2	0.30089987
p_3	0.003716462	p_3	0.00142961
p_4	0.018928669	p_4	0.03692484
p_5	$7.17288309 * 10^{-5}$	p_5	$4.1464406 * 10^{-4}$
p_6	0.98138568	-	-
p_7	$3.31033229 * 10^{-5}$	-	-
p_8	0.01758642	p_6	0.04036082
p_9	$2.56707631 * 10^{-6}$	p_7	$2.8118593 * 10^{-12}$
-	-	P_8	0.10928015
p_{10}	0.10927865	p_9	$4.3601980 * 10^{-14}$
p_{11}	$6.66091373 * 10^{-4}$	p_{10}	$6.42580655 * 10^{-6}$
p_{12}	$4.13286068 * 10^{-6}$	p_{11}	2.65330416
p_{13}	0.93794325	p_{12}	0.00503468
$S_I = \frac{p_3}{p_2}$	0.00165982	$S_I = \frac{p_3}{p_2}$	0.00475113
$S_E = \frac{p_7}{p_6}$	$3.37312064 * 10^{-5}$	-	-
$S_A = \frac{p_{12}}{p_{11}}$	0.006204645	$S_A = \frac{p_{10}}{p_9}$	$1.49667911 * 10^{8}$

B.4.2. 40% of VO^{max}

Parameter GEMM	Value	Parameter SGEMM	Value
p_1	$9.82210456 * 10^{-7}$	p_1	$1.294901545 * 10^{-4}$
p_2	2.174472150	p_2	3.046685906
p_3	0.030060071	p_3	0.026127559
p_4	0.427363226	p_4	0.155124835
p_5	$3.10209295 * 10^{-7}$	p_5	$2.03958405 * 10^{-7}$
p_6	0.351946257	-	-
p_7	$5.50234639 * 10^{-4}$	-	-
p_8	0.710810527	p_6	0.238400979
p_9	1.374827718	p_7	1.374827718
-	-	P_8	0.223552393
p_{10}	0.061870951	p_9	0.061870951
p_{11}	0.183857888	p_{10}	0.814572420
p_{12}	$8.78558488 * 10^{-4}$	p_{11}	0.001336112
p_{13}	0.314711184	p_{12}	0.362639165
$S_I = \frac{p_3}{p_2}$	0.013824077	$S_I = \frac{p_3}{p_2}$	0.008575731
$S_E = \frac{p_7}{p_6}$	0.001563405	-	-
$S_A = \frac{p_{12}}{p_{11}}$	0.004778465	$S_A = \frac{p_{10}}{p_9}$	13.16566828

B.4.3. 58% of VO^{max}

Parameter GEMM	Value	Parameter SGEMM	Value
$S_G = p_1$	0.20550317	p_1	0.016411558
p_2	1.13046419	p_2	0.963873328
p_3	0.02299561	p_3	0.000679837
p_4	0.09800001	p_4	0.010277818
p_5	0.05600000	p_5	$7.87208 * 10^{-14}$
p_6	5.37961561	-	-
p_7	0.00015838	-	-
p_8	1.59847556	p_6	0.161251435
p_9	9.20837923	p_7	0.016193108
p_{10}	0.09947311	p_8	0.001037968
p_{11}	0.00000188	p_9	0.099488025
p_{12}	0.00001003	p_{10}	0.010979608
p_{13}	6.40031140	p_{11}	0.000003678
-	0.02034174	p_{12}	2.681901231
$S_I = \frac{p_3}{p_2}$	0.00002944	$S_I = \frac{p_3}{p_2}$	0.000705317
$S_E = \frac{p_7}{p_6}$	5.32583804	-	-
$S_A = \frac{p_{12}}{p_{11}}$	0.20550317	$S_A = \frac{p_{10}}{p_9}$	0.110361102

B.4.4. 70% of VO^{max}

Parameter GEMM	Value	Parameter SGEMM	Value
$S_G = p_1$	0.21299553	p_1	0.346341523
p_2	1.29778516	p_2	9.633789789
p_3	0.03443631	p_3	$1.173031 * 10^{-4}$
p_4	0.24788057	p_4	14.231816526
p_5	0.01799555	p_5	8.603068353
p_6	0.09630926	-	-
p_7	0.00004806	-	-
p_8	1.43637670	p_6	0.001000000
p_9	0.22328702	p_7	23.707465199
-	-	P_8	3.124506262
p_{10}	0.30186851	p_9	0.953347919
p_{11}	0.07182015	p_{10}	$4.189026 * 10^{-6}$
p_{12}	0.00009171	p_{11}	$8.169374 * 10^{-4}$
p_{13}	1.73064711	p_{12}	4.454932251
$S_I = \frac{p_3}{p_2}$	0.02653468	$S_I = \frac{p_3}{p_2}$	$1.217621 * 10^{-5}$
$S_E = \frac{p_7}{p_6}$	$4.989975 * 10^{-4}$	-	-
$S_A = \frac{p_{12}}{p_{11}}$	0.00127690	$S_A = \frac{p_{10}}{p_9}$	$4.394016 * 10^{-6}$

B.6. T1DM Glucagon Exercise Minimal Model

Parameter	PVO_2^{max}			
	30%	**40%**	**58%**	**70%**
$S_G = p_1$	0.01027182	$5.016009 * 10^{-7}$	0.018207975	0.13696906
p_2	4.78573664	2.175737907	4.84584071	4.31249661
p_3	0.00346643	0.029688922	0.01947456	0.05050953
p_4	0.06522939	0.424544428	0.00736092	2.78760207
p_5	6.73082717	$4.549747 * 10^{-9}$	$1.33194 * 10^{-12}$	82.16969825
p_6	0.10781389	0.349566126	0.04045856	0.08585775
p_7	$2.32071 * 10^{-6}$	$5.43164 * 10^{-4}$	$2.550857 * 10^{-6}$	0.00002443
p_8	0.00351130	0.710479808	0.00785531	0.13772318
p_9	$2.17520 * 10^{-9}$	1.38473137	$4.840995 * 10^{-8}$	9.13487573
p_{10}	0.10927957	0.05874696	0.12256887	0.39720033
p_{11}	0.00104748	0.18290123	0.01581215	$3.340849 * 10^{-14}$
p_{12}	$2.55196 * 10^{-6}$	$8.73518 * 10^{-4}$	$3.773498 * 10^{-6}$	$9.456928 * 10^{-6}$
p_{13}	0.39720317	0.3254266	0.93952685	1.01646595
$S_I = \frac{p_3}{p_2}$	$7.24326 * 10^{-4}$	0.01364545	0.00401882	106.53106953
$S_E = \frac{p_7}{p_6}$	$2.15261 * 10^{-5}$	0.001553823	$6.304863 * 10^{-5}$	0.01171236
$S_A = \frac{p_{12}}{p_{11}}$	0.00243627	0.0047759	$2.386455 * 10^{-4}$	2.83069598

Appendix C Code Examples

C.1. MATLAB

C.1.1. IVGTT Linear Glucagon Minimal Model

Main

```
function [] = Molly_Glucagon_Model

format compact
format long

data = [0   92  11
        2   350 26
        4   287 130
        6   251 85
        8   240 51
        10  216 49
        12  211 45
        14  205 41
        16  196 35
        19  192 30
        22  172 30
        27  163 27
        32  142 30
        42  124 22
        52  105 15
        62  92  15
        72  84  11
        82  77  10
        92  82  8
        102 81  11
        122 82  7
        142 82  8
        162 85  8
        182 90  7];

t_data = data(2:length(data),1);
glucose_data = data(2:length(data),2);
insulin_data = data(2:length(data),3);

G_b = 92.5;
I_b = 13.2;
E_b = 142;

options = optimset('MaxFunEvals',10000,'MaxIter',5000,'TolX',1e-
4000,'TolFun',1e-4000);
guess = [  0.02
   0.05
    1.28e-005
   0.142
   0.002
   0.05
    2.9e-005
  0.02
   293
    3.6e+002];
```

```
lb = [0.008 0.05 0.000001 0.05 0.0005 0.01 0.000001 0.00001 279 360];
ub = [0.03 0.5 0.0001 0.5 0.05 0.0495 0.2 0.5 293 403];

model_param =
lsqnonlin(@Glucagon_Error_Func,guess,lb,ub,options,t_data,glucose_data,in
sulin_data,G_b,I_b,E_b);


tspan = 0:.5:max(t_data);

IC = [model_param(9),0,model_param(10),E_b];

sol = ode45(@Glucagon_system,tspan,IC,[],model_param,G_b,I_b,E_b);
disp('parameter values')
for i = 1:10
disp(model_param(i))
end
disp('S_I'),disp(model_param(3)/model_param(2))

final_soln = deval(sol,tspan);
G = final_soln(1,:);
X = final_soln(2,:);
I = final_soln(3,:);
E = final_soln(4,:);

disp('Do you wish to view G, X, I or E')
disp('1=Blood Glucose Level')
disp('2=Interstitial Insulin Level')
disp('3=Plasma Insulin Level')
disp('4=Plasma Glucagon Level')
plot_choice = input('');

if plot_choice == 1
    plot(t_data,glucose_data,'o')
    hold on
    plot(tspan,G,'g')
    ylabel('Plasma Glucose (mg/dL)')
    xlabel('Time (mins)')
    legend('Plasma Glucose Data IVGTT','Model for Plasma Glucose
Concentration IVGTT')
elseif plot_choice == 2
    plot(tspan,X,'--g')
    ylabel('Interstitial Insulin (1/min)')
    xlabel('Time (mins)')
    legend('Interstitial Insulin Activity IVGTT')
elseif plot_choice == 3
    plot(t_data,insulin_data,'o')
    hold on
    plot(tspan,I,'g')
    ylabel('Plasma Insulin (uU/mL)')
    xlabel('Time (mins)')
    legend('Plasma Insulin Data IVGTT','Model for Plasma Insulin
Concentration IVGTT')
elseif plot_choice == 4
    plot(tspan,E,'g')
    ylabel('Plasma Glucagon (pg/mL)')
    xlabel('Time (mins)')
    legend('Model for Plasma Glucagon Concentration IVGTT')
end
```

System of ODEs

```
function dydt = Glucagon_system(t,y,param,G_b,I_b,E_b)

if y(1)-G_b<=0
    F1 = 0;
    F2 = G_b-y(1);
else
    F1 = y(1)-G_b;
    F2 = 0;
end

if y(3)-I_b<0
    F3=0;
else
    F3=y(3)-I_b;
end
dydt = [-param(1)*(y(1)-G_b)-y(2)*y(1)+param(8)*(y(4)-E_b)
        -param(2)*y(2)+param(3)*F3
        -param(4)*(y(3)-I_b)+param(5)*F1*t
        -param(6)*(y(4)-E_b)+param(7)*F2*t];
```

Error Function

```
function error =
Glucagon_Error_Func(guess,t_data,glucose_data,insulin_data,glucagon_data,
G_b,I_b,E_b)

IC = [guess(9),0,guess(10),E_b];
tspan = 0:0.01:max(t_data);

sol = ode45(@Glucagon_system,tspan,IC,[],guess,G_b,I_b,E_b);
approx_soln = deval(sol,t_data);
glucose_approx = approx_soln(1,:);
insulin_approx = approx_soln(3,:);

N = length(glucose_data);
error = [glucose_data(3:N).'-glucose_approx(3:N) insulin_data(3:N).'-
insulin_approx(3:N)];
```

C.1.2. Glucagon Exercise Minimal Model for T1DM at 30% of VO^{max}

Main

```
function [] = Molly_Glucagon_Model

format compact
format long

data = [0   4.51*18 13.9    75
40  4.57*18 12.3    76
90  4.3*18  10  99
180 3.5*18  7.2 201
240 3.12*18 6.2 408];

t_data = data(1:length(data),1);
```

```
glucose_data = data(1:length(data),2);
insulin_data = data(1:length(data),3);
glucagon_data = data(1:length(data),4);

options = optimset('MaxFunEvals',1000,'MaxIter',5000,'TolX',1e-
400,'TolFun',1e-400);

guess = [ 0.01
   4.79
   0.0035
   0.065
   6.7
   0.11
    2.32e-006
   0.0035
    2.175e-009
   0.11
   0.00105
    2.55e-006
   0.397
    ];

lb = [0.008 0.5  0.00001 0.008  0  0.0002   0       0.00028 0 0.05 0   0
0];
ub = [1       5    1  0.5  100  3   0.00008    0.4   1  1   1   1  3];

G_b = 81.2;
I_b = 13.9;
E_b = 75;

model_param =
lsqnonlin(@Glucagon_Error_Func,guess,lb,ub,options,t_data,glucose_data,in
sulin_data,glucagon_data,G_b,I_b,E_b);

% CONFIDENCE INTERVAL OF PARAM FITTING
[x,resnorm,residual,exitflag,output,lambda,jacobian] =
lsqnonlin(@Glucagon_Error_Func,guess,lb,ub,options,t_data,glucose_data,in
sulin_data,glucagon_data,G_b,I_b,E_b);
ci = nlparci(x,residual,jacobian,0.05);
disp('Parameter confidence intervals')
disp(ci)
t = tinv(0.95/2,length(data)-length(x));
se = (ci(:,2)-ci(:,1)) ./ (2*t);
disp('standard error'),disp(se)


tspan = 0:0.01:max(t_data);
IC = [G_b,0,I_b,0,E_b,500,0,0];

sol = ode45(@Glucagon_system,tspan,IC,[],model_param,G_b,I_b,E_b);

disp('parameter values')
for i=1:13
    disp(model_param(i));
end
disp('Insulin Sensitivity'),disp(model_param(3)/model_param(2))
disp('Glucagon Sensitivity'),disp(model_param(7)/model_param(6))
disp('Exercise Sensitivity'),disp(model_param(12)/model_param(11))

final_soln = deval(sol,tspan);
G = final_soln(1,:);
X = final_soln(2,:);
```

```
I = final_soln(3,:);
Y = final_soln(4,:);
E = final_soln(5,:);
gly = final_soln(6,:);
pvo2max = final_soln(7,:);
exac = final_soln(8,:);

disp('Do you wish to view G, X, I, Y or E')
disp('1=Blood Glucose Level')
disp('2=Interstitial Insulin Level')
disp('3=Plasma Insulin Level')
disp('4=Glucagon Activity')
disp('5=Plasma Glucagon Level')
disp('6=Glycogen')
disp('7=pvo2max')
disp('8=Exercise Activity')
plot_choice = input('');
if plot_choice == 1
    plot(t_data,glucose_data,'o')
    hold on
    plot(tspan,G,'b')
    ylabel('Plasma Glucose (mg/dl)')
    xlabel('Time (minutes)')
    legend('Plasma Glucose Samples','Plasma Glucose Concentration')
elseif plot_choice == 2
    plot(tspan,X,'--b')
    xlabel('Time (minutes)')
    ylabel('Interstitial Insulin 1/min')
elseif plot_choice == 3
    plot(t_data,insulin_data,'o')
    hold on
    plot(tspan,I,'b')
    xlabel('Time (minutes)')
    ylabel('Plasma Insulin (uU/ml)')
    legend('Plasma Inslulin Samples','Plasma Insulin Concentration')
elseif plot_choice == 4
    plot(tspan,Y,'--b')
    ylabel('Glucagon Action 1/min')
    xlabel('Time (minutes)')
elseif plot_choice == 5
    plot(tspan,E,'b')
    hold on
    plot(t_data,glucagon_data,'o')
    ylabel('Glucagon (pg/ml)')
    xlabel('Time (minutes)')
    legend('Plasma Glucagon Samples','Plasma Glucagon Concentrations')
elseif plot_choice == 6
    plot(tspan,gly,'b')
    ylabel('Muscle Glycogen (g)')
    xlabel('Time (minutes)')
    legend('Amount of Glycogen Available in Skeletal Muscle (g)')
elseif plot_choice == 7
    plot(tspan,pvo2max,'b')
    ylabel('PVO2max (%)')
    xlabel('Time (minutes)')
    legend('Percentage of VO2max')
elseif plot_choice == 8
    plot(tspan,exac,'--b')
    ylabel('Exercise Action 1/min')
    xlabel('Time (minutes)')
end
```

System of ODEs

```
unction dydt =

Glucagon_system(t,y,param,G_b,I_b,E_b) Exdur = 240;

if t > 0 && t <
    Exdur u3 = 30;
else
    u3 = 0;
end

if y(1)>=G_b
    F1 = y(1)-G_b;
else
    F1 = 0;
end

if y(1)<=G_b
    F2 = G_b-y(1);
else
    F2 = 0;
end
ton =  240;
tdeg = 1200;
IexgL = param(5)*(-exp(-pi*(t+780)/ton)+exp(-pi*(t+780)/tdeg));


dydt = [-param(1)*(y(1)-G_b)-y(1)*(y(2)-
y(4)+y(8))+param(13)*(y(7)*y(6)*param(10))/(250+y(6))
        -param(2)*y(2)+param(3)*y(3)
        -param(4)*(y(3))-(y(8)*y(3))+IexgL
        -param(6)*y(4)+param(7)*y(5)
        -param(8)*(y(5)-E_b)+param(9)*F2+y(5)*y(8)
        -(y(7)*y(6)*param(10))/(250+y(6))
        -0.8*y(7)+0.8*u3
        -param(11)*y(8)+param(12)*y(7)];
```

Error Function

```
function error =
Glucagon_Error_Func(guess,t_data,glucose_data,insulin_data,glucagon_data,
G_b,I_b,E_b)

IC = [G_b,0,I_b,0,E_b,500,0,0];
tspan = 0:0.01:max(t_data);

sol =
ode45(@Glucagon_system,tspan,IC,[],guess,G_b,I_b,E_b);
approx_soln = deval(sol,t_data);
glucose_approx = approx_soln(1,:);
insulin_approx = approx_soln(3,:);
glucagon_approx =
approx_soln(5,:);

N = length(glucose_data);
error = [glucose_data(1:N).'-glucose_approx(1:N)
insulin_data(1:N).'- insulin_approx(1:N) glucagon_data(1:N).'-
glucagon_approx(1:N)];
```

C.2. Mathematica Characteristic Equations and Eigen Values

C.2.1. Linear Glucagon Exercise Minimal Model