OPTIMAL SAMPLING SCHEDULE FOR MEASURING INSULIN SENSITIVITY INDEX FROM ORAL GLUCOSE TOLERANCE TEST DATA

THANATIP CHANKONG

A THESIS SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR
THE DEGREE OF MASTER OF ENGINEERING
(BIOMEDICAL ENGINEERING)
FACULTY OF GRADUATE STUDIES
MAHIDOL UNIVERSITY
2007

Thesis
Entitled

OPTIMAL SAMPLING SCHEDULE FOR MEASURING INSULIN SENSITIVITY INDEX FROM ORAL GLUCOSE TOLERANCE TEST DATA

.....
Miss. Thanatip Chankong
Candidate

.....
Assist.Prof. Chatchai Neatpisarnvanit,
Ph.D. (Electrical Engineering)
Major-Advisor

.....
Prof. Boonsong Ongphiphadhanakul,
M.D.
Co-Advisor

.....
Prof. M.R. Jisnuson Svasti,
Ph.D.
Dean
Faculty of Graduate Studies

.....
Assist.Prof. Theeraporn Rubcumintara,
Ph.D. (Materials Engineering & Science)
Chair
Master of Engineering Programme in
Biomedical Engineering
Faculty of Engineering

Thesis
Entitled

OPTIMAL SAMPLING SCHEDULE FOR MEASURING INSULIN SENSITIVITY INDEX FROM ORAL GLUCOSE TOLERANCE TEST DATA

was submitted to the Faculty of Graduate Studies, Mahidol University
for the degree of Master of Engineering (Biomedical Engineering)
on
25 May, 2007

.....
Miss. Thanatip Chankong
Candidate

.....
Assist.Prof. Bovornlak Oonkhanond,
Ph.D. (Chemical Engineering)
Chair

.....
Assist.Prof. Chatchai Neatpisarnvanit,
Ph.D. (Electrical Engineering)
Member

.....
Admiral Dr. Paibul Nacaskul,
Ph.D. (Electrical Engineering)
Member

.....
Prof. Boonsong Ongphiphadhanakul,
M.D.
Member

.....
Prof. M.R. Jisnuson Svasti,
Ph.D.
Dean
Faculty of Graduate Studies
Mahidol University

.....
Assist.Prof. Piya Rattanasuwan,
M.Eng.
Dean
Faculty of Engineering
Mahidol University

ACKNOWLEDGEMENT

I would like to thank my major advisor, Asst. Prof. Dr. Chatchai Neatpisarnvanit, for his academic assistance, valuable guidance and encouragement throughout my master study. I gratefully thank my co-advisor, Prof. Boonsong Ongphiphadhanakul, for his suggestion for improving this dissertation. I would also like to thank all the members of the advisory committee, Assist.Prof. Bovornlak Oonkhanond and Admiral Dr. Paibul Nacaskul, for their kindness and valuable suggestions.

I would like to give my thanks to all my teachers, friends and staffs at department of Biomedical Engineering for all the support. I also thank my friends at department of Mechanical Engineering, Chiangmai university, for their suggestion, and encouragement.

I would like to sincerely thank my mom for her greatest love, valuable suggestions and encouragement. I thank my dad who taught me to be strong , my grandma and my sister for their greatest love and encouragement. I also thank my brother for his assistance in editing this thesis.

Thanatip Chankong

OPTIMAL SAMPLING SCHEDULE FOR MEASURING INSULIN SENSITIVITY INDEX FROM ORAL GLUCOSE TOLERANCE TEST DATA

THANATIP CHANKONG 4736131 EGBE/M

M. Eng. (BIOMEDICAL ENGINEERING)

THESIS ADVISORS: CHATCHAI NEATPISARNVANIT, Ph.D. (ELECTRICAL ENGINEERING), BOONSONG ONGPHIPHADHANAKUL, M.D.

ABSTRACT

Insulin sensitivity index (S_I) is an index that measures the ability of insulin to reduce the increase of glucose in blood. This index is useful for diagnosis and evaluation of the efficacy of diabetic therapy. Among many methods of evaluating S_I, The Oral Glucose Tolerance Test (OGTT) is a commonly used method not only because it is close to physiological condition but it is also simple and inexpensive. The S_I of OGTT data can be estimated from the well known mathematical model called the minimal model coupled with the glucose absorption model. The major disadvantage of the minimal model is the number of blood samples required for parameter estimation process.

The aim of this study was to develop the optimal sampling schedule for OGTT data. This sampling schedule minimizes the number of samples required while maintaining the estimation error not to exceed 5 percent of S_I estimated from full sampling schedule. This study focused on computer simulation. Glucose-insulin profile of normal glucose tolerance (NGT) data was generated from a mathematical model implemented on MATLAB©. The reduced sampling schedule (RSS) at various numbers of samples were selected using Simulated Annealing optimization method. S_I of each RSS (S_I^{RSS}) was estimated for all data types. The optimal sampling schedule (OSS) was selected from the RSS which S_I error was less than 5 percent and had minimum number of samples. Data with Gaussian noise was tested to evaluate robustness of the algorithm. The RSS was validated with human experiment data. The optimal sampling schedule for simulated data is at 7 samples. The optimal number of samples from human experiment data was found to be subject-specific. The average sample number for human experiments is at 8 samples. The results showed that the time point at maximum glucose concentration is important for insulin sensitivity index estimation.

KEY WORDS: INSULIN SENSITIVITY INDEX/ ORAL GLUCOSE MINIMAL MODEL/ OPTIMAL SAMPLING SCHEDULE/ SIMULATED ANNEALING

81 pp.

ตารางเวลาการเจาะเลือดที่เหมาะสมเพื่อประมาณค่าดัชนีวัดความไวของอินซูลินจากการทดสอบความทนของร่างกายต่อการบริโภคน้ำตาล (OPTIMAL SAMPLING SCHEDULE FOR MEASURING INSULIN SENSITIVITY INDEX FROM ORAL GLUCOSE TOLERANCE TEST DATA)

ธนาทิพย์ จันทร์คง 4736131 EGBE/M
วศ.ม. (วิศวกรรมชีวการแพทย์)
คณะกรรมการควบคุมวิทยานิพนธ์ : ฉัตรชัย เนตรพิศาลวนิช, Ph.D. (Electrical Engineering), บุญส่ง องค์พิพัฒนกุล, M.D.

บทคัดย่อ

ดัชนีวัดความไวอินซูลินเป็นดัชนีชี้วัดความสามารถของอินซูลินในการลดระดับน้ำตาลในเลือดที่สูงขึ้น มีประโยชน์ในการช่วยวินิจฉัยและประเมินประสิทธิภาพในการให้การรักษาผู้ป่วยเบาหวาน การคำนวณค่าดัชนีความไวอินซูลินจากการทดสอบความทนได้ต่อน้ำตาลที่บริโภคเป็นวิธีการที่นิยมใช้แพร่หลายเนื่องจากเป็นวิธีที่ง่ายและราคาถูก นอกจากนี้ยังเป็นวิธีการทดสอบที่ใกล้เคียงกับสภาวะร่างกายปกติ ดัชนีความไวจากการทดสอบด้วยการกินน้ำตาลสามารถคำนวณได้จากแบบจำลองคณิตศาสตร์ที่เรียกว่า Minimal Model ร่วมกับแบบจำลองการดูดซึมน้ำตาลจากการกินเข้าสู่กระแสเลือด ข้อเสียของการใช้แบบจำลอง Minimal Model คือจำเป็นต้องใช้ตัวอย่างเลือด ณ จุดเวลาต่างๆจำนวนมากเพื่อใช้ในการประมาณค่าจากแบบจำลอง จุดประสงค์ของวิทยานิพนธ์นี้คือเพื่อพัฒนาตารางเวลาการเจาะเลือดแบบใหม่สำหรับการทดสอบความทนได้ของระดับน้ำตาลจากการบริโภค ตารางเวลาดังกล่าวมีจำนวนการเจาะตัวอย่างเลือดที่น้อยครั้งแต่ยังคงสามารถใช้คำนวณค่าดัชนีความไวอินซูลินได้โดยมีความผิดพลาดไม่เกิน ร้อยละ 5 จากการคำนวณด้วยการใช้ตัวอย่างเลือดจำนวนมาก งานศึกษานี้จะใช้การจำลองผลด้วยคอมพิวเตอร์เป็นหลัก ข้อมูลกลูโคสและอินซูลินที่ใช้ในการศึกษาเป็นข้อมูลที่ได้จากการสร้างด้วยคอมพิวเตอร์ ซึ่งประกอบด้วยข้อมูลของประชากรที่มีความทนได้ต่อน้ำตาลเป็นปกติ การหาตารางเวลาการเจาะเลือดแบบจำนวนตัวอย่างน้อยใช้วิธีการคำนวณด้วย Simulated Annealing Optimization เพื่อหาตารางเวลาที่เหมาะสม ข้อมูลกลูโคสถูกเพิ่มสัญญาณรบกวนเพื่อทดสอบความคงทนต่อความแปรปรวนในสัญญาณ รวมถึงการทดสอบกับข้อมูลที่ได้จากการทดลองการบริโภคน้ำตาลในคน

ตารางการเจาะเลือดที่เหมาะสมสำหรับข้อมูลที่จำลองขึ้นเองประกอบด้วยการเจาะเลือด 7 ครั้ง ผลการทดลองกับข้อมูลจริงพบว่าจำนวนที่เหมาะสมขึ้นอยู่กับแต่ละบุคคล ข้อมูลที่สำคัญต่อการประมาณค่าดัชนีควรมีข้อมูล ณ เวลาที่ความเข้มข้นกลูโคสมีค่าสูงที่สุด

81 หน้า

CONTENTS

		Page
ACKNOWLEDGMENT		**iii**
ABSTRACT (ENGLISH)		**iv**
ABSTRACT (THAI)		**v**
LIST OF TABLES		**viii**
LIST OF FIGURES		**ix**
LIST OF ABBREVIATIONS		**ix**
CHAPTER		
I	**INTRODUCTION**	1
	1. Background	1
	2. Research Objective	2
	3. Thesis Organization	2
II	**LITERATURE REVIEWS**	4
	1. Physiology of Glucose Metabolism	4
	2. Methods for Measuring Insulin Resistance	10
	3. The Minimal Model for Glucose Kinetics	14
	4. Rate of Glucose Absorption from Oral Glucose Tolerance Test	17
	5. The Minimal Model with Reduced Sampling Schedule	20
	6. Reduced Sampling Schedule Optimization	21
III	**MATERIALS AND METHODS**	24
	1. Insulin Sensitivity Index Estimation	28
	2. Selecting Reduced Sampling Schedule by Simulated Annealing	29
	3. Experimental Methodology	33

CONTENTS (Continued)

		Page
IV	**EXPERIMENTAL RESULTS**	39
	1. Characteristics of the Proposed Simulated Annealing Algorithm	39
	2. Optimal Number of Sample and OSS of Simulated Data	43
	3. Monte Carlo Simulation	45
	4. Validation of the RSS with Human Experiment Data	47
V	**DISCUSSION**	50
	1. Performance of the Simulated Annealing Algorithm of Optimal Sampling Schedule Problem	50
	2. Reduced Sampling Schedule from Simulated Annealing Algorithm	51
	3. Optimal Number of Sample and Optimal Sampling Schedule of Simulated Data	53
	4. Validation with Human Experiment Data	55
VI	**CONCLUSION AND FURTHER DEVELOPMENTS**	57
REFERENCES		59
APPENDIX		63
BIOGRAPHY		81

LIST OF TABLES

Table **Page**

1. S_I^{RSS} values estimated from RSS obtained from different objective function 40
2. Control parameter for the proposed SA 41
3. Minimum energy, final energy and performance error of RSS 42
4. S_I^{RSS} and percentage error of NGT data 43
5. Mean RSS with different numbers of sample 44
6. Statistical values of each sample in OSS from Monte Carlo simulation 46
7. Individual RSS of subject 1 47
8. Individual RSS of subject 2 47
9. Individual RSS of subject 3 48

LIST OF FIGURES

Figure **Page**

1. Glucose metabolism diagram 5
2. Schematic diagram of carbohydrate digestion 6
3. Regulation of Blood Glucose Concentrations 8
4. Rates of total, meal, and endogenous glucose appearance in circulation during a 6 hours postprandial period 8
5. Disordered plasma glucose homeostasis in insulin deficiency 9
6. The model derived for calculating insulin sensitivity index using area under curve method 12
7. The physiological regulation used to interpret the IVGTT test 15
8. The minimal model for glucose kinetics 15
9. The oral minimal model in combination with Steele's estimation of gut-glucose appearance as an input 17
10. Rate of glucose absorption simulated from the oral minimal model 25
11. Diagram of the oral minimal model 25
12. Diagram of glucose absorption model 26
13. Simulated glucose profiles of NGT data. 26
14. The overall procedure of the research work 27
15. Parameter estimation process 28
16. SA algorithms for selecting reduced sampling schedule 30
17. Process of generating new sampling schedule 31
18. Model sensitivity with respect to model parameters of NGT subject 33
19. Sampling schedule diagram of 3 human experiment data sets 37
20. Glucose and insulin concentration from human experiment data 38

LIST OF FIGURES (Continued)

Figure **Page**

21. Percentage error of S_I^{RSS} obtained from different weight functions 40
22. The number of accepted schedule at each temperature and the energy of accepted schedule as the number of iteration increase 41
23. Minimum and final energy of RSS obtained from the SA at each number of samples in schedule 42
24. Percentage error of S_I from RSS at different number of sample. The red dash line represented the percentage error bound of OSS 44
25. Boxplot of distribution of time point in sampling schedule from Monte Carlo Simulation 45
26. The robustness of OSS against noise 46
27. Individual OSS with 6 samples of subject 1 48
28. Individual OSS with 9 samples of subject 2 49
29. Individual OSS with 10 samples of subject 3 49
30. Ten-sample sampling schedule diagram obtained from a) obj_p1 b) obj_u 52
31. RSS diagram of 10 samples 54

LIST OF ABBREVIATIONS

DM	Diabetes Mellitus
IDDM	Insulin-Dependent Diabetes Mellitus
NIDDM	Non Insulin-Dependent Diabetes Mellitus
IVGTT	Intravenous Glucose Tolerance Test
OGTT	Oral Glucose Tolerance Test
S_I	Insulin Sensitivity Index
EGP	Endogenous Glucose Production
ATP	Adenosine triphosphate
GLUT	Glucose transporters
HOMA	Homeostasis Model Assessment
QUICKI	Quantitative Insulin-sensitivity Check Index
AUC	area under curve
R_{HOMA}	HOMA insulin resistance
NHGB	net hepatic glucose balance
Ra(t)	rate of glucose appearance in plasma
FSS	Full sampling schedule
RSS	reduced sampling schedule
OSS	Optimal sampling schedule
SA	simulated annealing algorithm
NGT	Normal Glucose Tolerance
IGT	Impaired Glucose Tolerance
S_I^{FSS}	Insulin Sensitivity Index of full sampling schedule
S_I^{RSS}	Insulin Sensitivity Index reduced sampling schedule

CHAPTER I
INTRODUCTION

1. Background

Diabetes Mellitus is a metabolism disorder resulted from abnormality of insulin production or insulin usage, a hormone released from pancreas to regulate glucose concentration in blood. There are two major types of Diabetes: type I or Insulin-dependent Diabetes Mellitus (IDDM), and type II or Non-insulin-dependent diabetes mellitus (NIDDM). Type I diabetes occurs when the pancreas is damaged by the immune system of the body which results in the loss of insulin production and is usually more severe than type II. Patient with type I diabetes needs insulin injection to control blood glucose. Eighty percent of diabetes patients are type II diabetes which is characterized by two defects; the insulin is produced insufficiently and peripheral tissues are less sensitive to the insulin (insulin resistance). The numbers of diabetic patients tend to increase in every region of the world. In 2003, around 194 million people have diabetes and it is estimated that the number will increase to 333 million by 2025 [1]. A problem of diabetic patient is not only the abnormality of blood glucose, but it also leads to many complications such as blindness, kidney failure, and poor circulation in lower limbs. It is also related to cardiovascular disease which is the first cause of death in Type II diabetic patients. Several researchers have been working on measuring insulin sensitivity, the ability of insulin to control glucose production and utilization. The index is useful for diagnosis and evaluation of the efficacy of therapy. The euglycemic hyperinsulinmic clamp technique is said to be the gold standard method of measuring insulin sensitivity index. However, clamp technique is not suitable for clinical use because of its high cost and complex procedure. Intravenous glucose tolerance test (IVGTT) is a technique to monitor the dynamic physiological response to IV glucose injection. The widely accepted method

to assess the IVGTT information is the minimal model developed by Bergman et. al. [2] The model is termed “minimal model” because it is the mathematical model with the fewest parameters which fit well with the data. The disadvantages of the IVGTT are that injecting a bolus of glucose directly into the blood perturbs the normal physiology of the body. Therefore, The IVGTT is unable to present the normal life condition. Moreover, insulin secretion does not depend solely on glucose appearance in blood, but also depends on other factors such as stimulation via glucose absorption in the gut. Oral glucose tolerance test (OGTT) is the common method used to evaluate the glucose tolerance of the body because it is close to the normal physiological system. Several models of the rate of ingested glucose that appears in the blood circulation has been proposed and used as an input to the classical minimal model. The major disadvantage of oral glucose minimal model is that the standard protocol of the number of sample needed for identification of minimal model is at least 30 samples over 4-5 hours which is not suitable for clinical use and epidemiological studies. The study protocol with shorter study period and fewer numbers of samples will benefit the use of minimal model as a powerful tool for clinical diagnosis and treatment.

2. Research Objectives

The aim of this research is to develop the new sampling schedule for oral glucose tolerance test with optimal protocol. The optimal protocol will minimize the number of samples required while maintaining the percentage error not to exceed the specific error bound which is 5 percent of insulin sensitivity index estimated from full sampling schedule.

3. Thesis Organization

This thesis consists of six chapters. Chapter 2 gives details of glucose-insulin mechanism in both physiological and mathematical aspects. This chapter also reviews various methods for measuring insulin resistance and discusses advantages and

disadvantages of each method. Studies related to the reduced sampling schedule are also summarized in this chapter. Chapter 3 explains the research methodology including estimating parameter and selecting reduced sampling schedule by simulated annealing algorithm. Chapter 4 describes the results. Discussion and conclusion are described in chapter 5 and 6, respectively.

CHAPTER II
LITERATURE REVIEWS

This chapter reviews the process of glucose regulation system of human body and the mathematical models as related to this system. The chapter begins with the description of how the ingested meal is converted into glucose and then metabolized. Next topic explains how the body regulates the glucose level in blood and the abnormality of blood glucose regulation mechanism followed by methods of measuring the defect in glucose regulation, in particular, "the minimal model" for oral glucose tolerance test. The rate of glucose absorption model which is used as the input to the minimal model is then described. The research works related to the oral glucose minimal model, the rate of glucose appearance model and the reduced sampling schedule for the minimal model are summarized in the final part of this chapter.

1. Physiology of Glucose Metabolism

Glucose is a crucial energy source of the human body. The main source of glucose for the body is gut. Glucose is absorbed at the intestine after ingestion of the meal while the liver produces glucose endogenous glucose production (EGP) to replace the glucose taken up by the body tissues during overnight fasting. Glucose production process is depicted in Figure 1. There are two mechanisms of glucose production at the liver: glycogenolysis and glucoseneogenesis. Glycogenolysis is the process that liver glycogen is degraded and released as glucose in the circulation during fasting. Gluconeogenesis is the new formation of glucose from noncarbohydrate precursors, mainly lactate, alanine and glycerol.

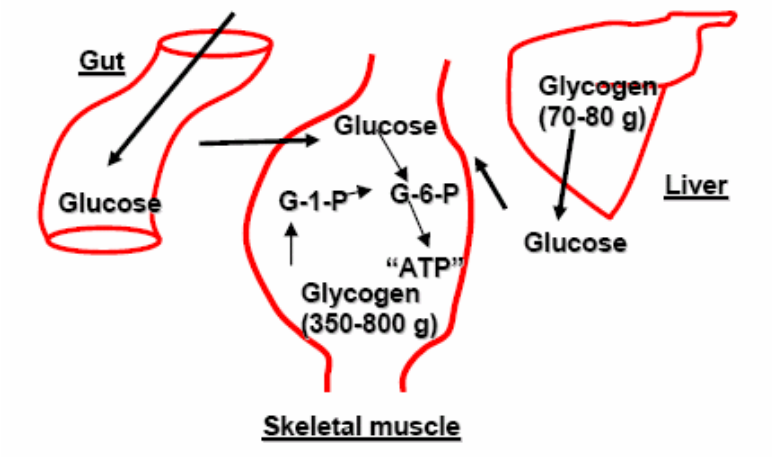


Figure 1 Glucose metabolism diagram. Gut and liver act as glucose sources for the body. Glucose is used as energy source: Adenosine triphosphate (ATP) is derived from glycolysis and mitochondrial oxidation of pyruvate. Excess glucose is stored in liver and skeletal muscle in the form of glycogen [3] .

In healthy persons there are three important mechanisms that control the increase of blood glucose concentration:

1. Stimulation of the insulin production by the pancreas,
2. Increase glucose uptake by body tissue,
3. Suppression of the hepatic glucose production.

1.1 Digestive system and digestion of carbohydrate

Digestive system consists of the following steps; food is ingested through the mouth and passes through the digestive tract. The tongue, the teeth and the digestive tract process the solid food mechanically. The food is then digested into small organic fragments (e.g. glucose) by the secreted acids and enzymes. Small organic molecules are then absorbed across the digestive wall into interstitial fluid of the digestive tract. The schematic diagram of carbohydrate digestion is depicted in Figure 2.

All carbohydrates in food are absorbed in the form of monosaccharide which is mostly glucose. This digested monosaccharide is absorbed through intestinal membrane into blood circulation and is delivered to the liver through hepatic portal system. The hepatic portal vessel contains substances absorbed directly from the digestive tract, therefore, level of glucose in the hepatic portal vein is often higher

than anywhere else in the circulation system. The portal system prevents the content in the system from mixing with the entire bloodstream.

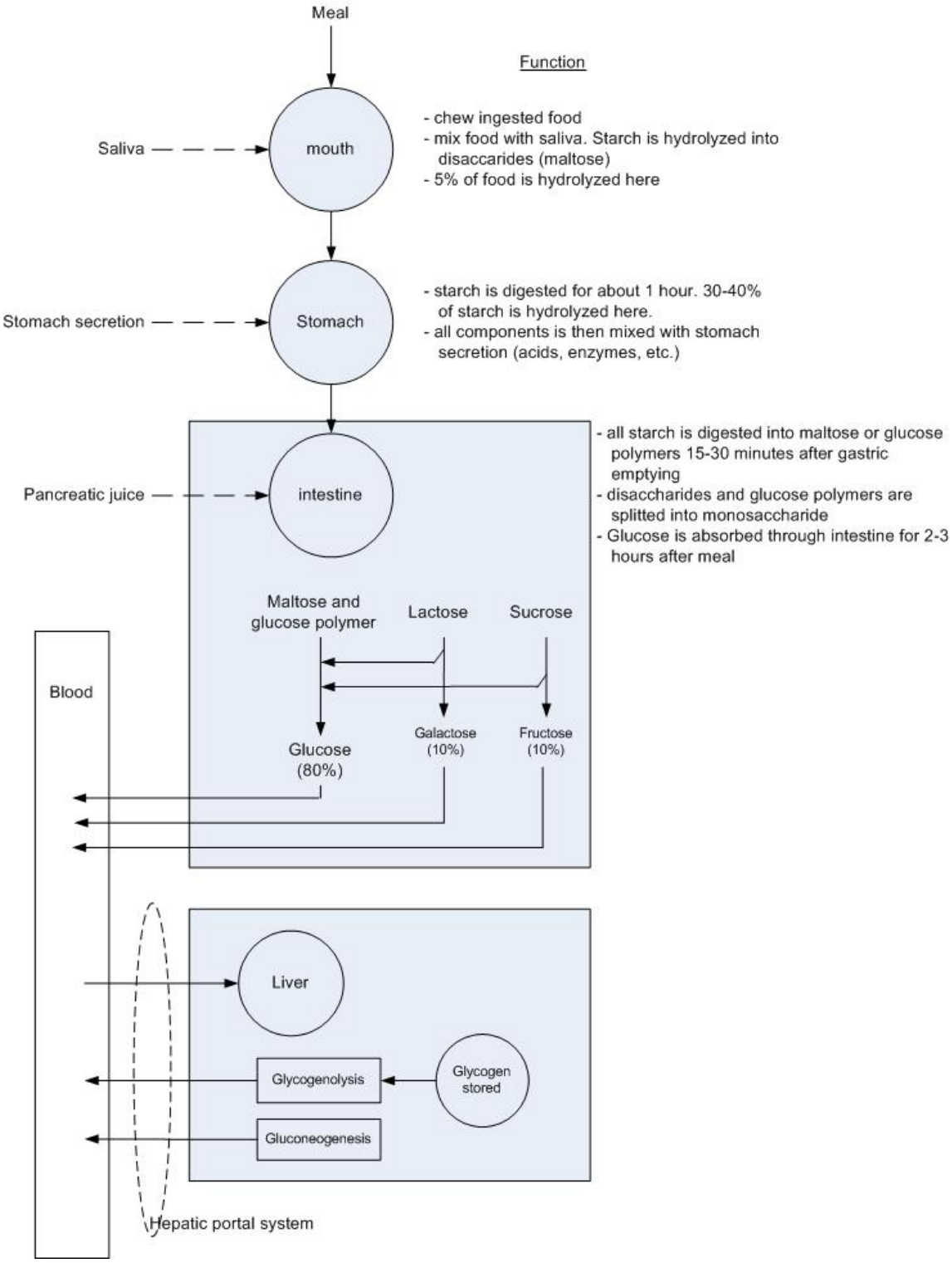


Figure 2 Schematic diagram of carbohydrate digestion

1.2 Regulation of blood glucose

Even though most tissues can utilize fats and proteins for energy when lack of glucose, some parts of the body, such as brain and retina, depend only on energy from glucose. Too high glucose level in blood can be dangerous to the body by causing dehydration in cells, loss of glucose in urine and damage to many tissues, especially blood vessels which can lead to increase risk of heart attack, stroke and blindness. Therefore, glucose concentration in blood is necessary to be maintained at a sufficient level. To regulate blood glucose level, the pancreas releases two hormones; insulin and glucagons which play important roles in controlling glucose level in blood. When blood glucose rises, insulin is released to facilitate glucose transport into cells. Insulin also increases the conversion of glucose to glycogen and stores it in liver (glucogenesis process). When glucose level declines, insulin secretion is suppressed and glucagon is released. Glucagon facilitates the breakdown of glycogen in skeletal muscles and liver cells to glucose (glycogenolysis process), and stimulates the breakdown of fatty acids and protein. Liver converts the lipids and amino acids to glucose and release into the circulation. This makes the glucose concentration rise back to normal level. Figure 3 shows the mechanism of regulation of blood glucose level.

During fasting period, the main energy source for the body is from endogenous glucose production by the liver. In postprandial state (i.e. after having a meal) the glucose level increased. The liver reduces this postprandial hyperglycemia via two mechanisms; increasing glucose uptake in all tissues and suppressing endogenous glucose production. In normal individual, about 25% of oral glucose is taken up by splanchnic tissues (gut and liver). Muscle uptake is about 25-56% [4]. The rest of glucose is cleared by other tissues which is non insulin sensitive. It is found that the endogenous production is suppressed by about 60% during postprandial state [5]. Figure 4 shows rates of total, meal, and endogenous glucose appearance in circulation.

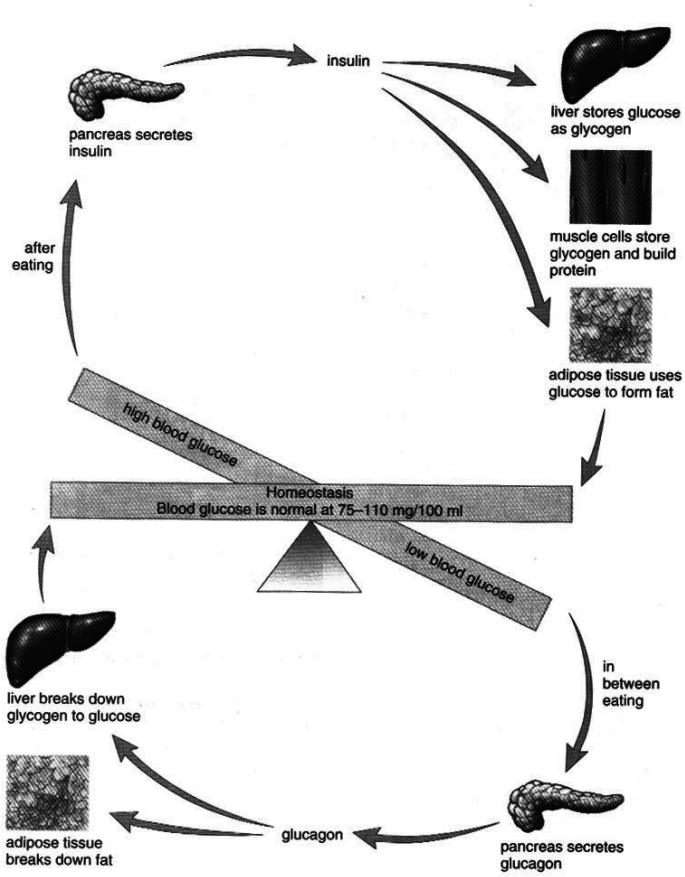


Figure 3 Regulation of Blood Glucose Concentrations [6].

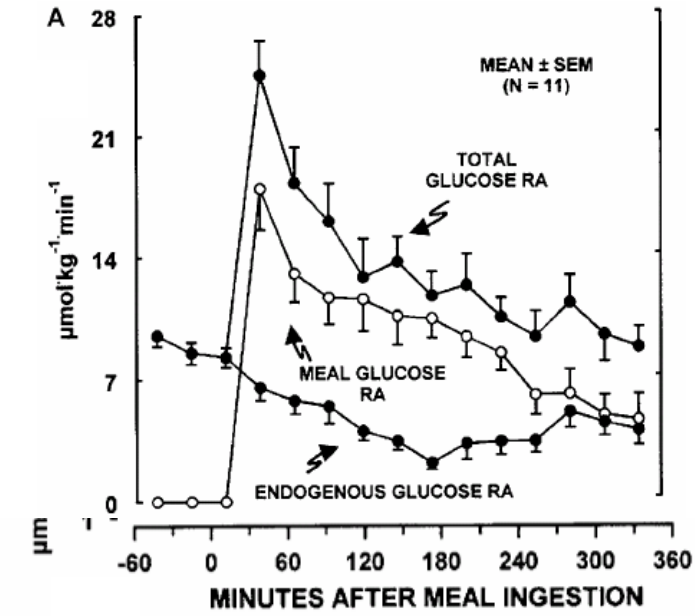


Figure 4 Rates of total, meal, and endogenous glucose appearance in circulation during a 6 hours postprandial period [5].

1.3 Insulin

Insulin is a hormone that plays a role in the metabolism of glucose. Insulin has ability to stimulate glucose uptake by skeletal muscle by increasing the amount of GLUT-4 on the cell surface. Insulin also increases total blood flow to skeletal muscle tissue which results in the increased delivery of insulin and glucose to cells [7]. Some tissues such as nervous system are insulin independent. The glucose uptake of the brain cells depends only on glucose concentration in circulation [8] . The rate of glucose uptake in this type of tissues does not change when insulin occurs. This ability of glucose itself to facilitate its own metabolism is called "glucose effectiveness". In other words, glucose effectiveness means the results of glucose transport by passive diffusion and carrier mediated transport at basal insulin levels.

Type II diabetes develops when the body does not respond to insulin, so called "insulin resistance". Insulin resistance elevates plasma glucose level which stimulates insulin secretion until it exceeds the limit. At this point, the basal insulin level is elevated. The effect of insulin on glucose utilization is expressed as the metabolic index called "insulin sensitivity". Figure 5 depicts the effect of insulin deficiency on glucose homeostasis. Measuring insulin sensitivity index is very important for assessing the efficiency of glucose regulatory system.

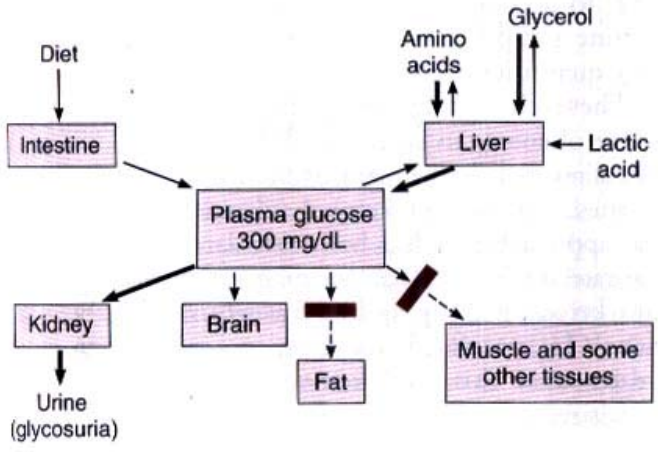


Figure 5 Disordered plasma glucose homeostasis in insulin deficiency. The heavy arrows indicate reactions that are accentuated. The rectangles across arrows indicate reaction that are blocked [9].

2. Methods for Measuring Insulin Resistance

There are two broad approaches to measure insulin sensitivity [10]: The dynamic intervention (glucose and insulin injection or infusion) and the steady state assessment (usually fasting state). The steady state indexes are, for example, Homeostasis Model Assessment (HOMA) and Quantitative Insulin-sensitivity Check Index (QUICKI).The examples of dynamic indexes group are the euglycemic hyperinsulinemic glucose clamp and glucose tolerance test.

2.1 Steady state assessment methods

The steady state assessment uses basal fasting glucose and insulin level to avoid the complexity of changing in glucose level. They are suitable for measuring sensitivity index among population due to its simplicity and low cost. The assessment in this group involves Homeostasis model assessment (HOMA), Quantitative Insulin-sensitivity Check Index (QUICKI) and the Area Under Curve (AUC).

2.1.1 Homeostasis Model Assessment (HOMA)

This method was developed from the feedback system of glucose-insulin interaction. In patient with insulin resistance, the plasma glucose and insulin concentration is higher than normal. In steady state condition, the glucose-insulin system will compensate the insulin resistance by increasing the insulin basal level. The HOMA insulin resistance is defined as the ratio of actual insulin level of the subject divided by the insulin level in a standard subject [11].

The assumption of HOMA is that the normal weight healthy subjects, aged less than 35 year,s have insulin resistance of 1 and beta cell function at 100%. The formula for HOMA insulin resistance (R_{HOMA}) and insulin sensitivity index is

$$R_{HOMA} = \frac{g \cdot i}{22.5} \qquad SI_{HOMA} = \frac{22.5}{(g \cdot i)} \tag{1}$$

where g is fasting plasma glucose [mmol/l]
i is fasting plasma insulin [μU/ml]

2.1.2 Quantitative Insulin-sensitivity Check Index (QUICKI)

QUICKI is obtained by examining the fasting data and choosing the best equation that best correlates to sensitivity index derived from clamp method [12]. The formula of QUICKI is

$$\text{or } SI_{QUICKI} = \frac{1}{\left[\log\left(HOMA\right) + \log\left(22.5\right)\right]} \tag{2}$$

Where I_0 is fasting plasma insulin [μU/ml]
G_0 is fasting plasma glucose [mmol/l]

2.1.3 Insulin sensitivity index from Area Under Curve (AUC)

The assumption of this method is that the postloading plasma glucose concentration without insulin is the summation of the glucose from liver, unused glucose and the peripheral glucose utilization. The glucose from liver and unused glucose is determined from the area under the glucose curve. The postloading plasma glucose concentration without insulin comes from the basal plasma glucose and the plasma glucose concentration after ingesting and without the insulin. The insulin sensitivity index is the ratio between the glucose disposal rate and the area under the insulin curve and is calculated by the following equation.

$$SI_{OGTT} = \left[1.9/6 \times BW \times FPG + 520 - 1.9/18 \times BWxAUCglu - Uglu/1.8\right] \times 1000/\left(AUCins \times BW\right) \tag{3}$$

where BW is body weight
FPG is fasting plasma glucose concentration
AUCglu is area above the glucose curve
Uglu is glucose appearing in the urine
AUCins is area under the insulin curve.

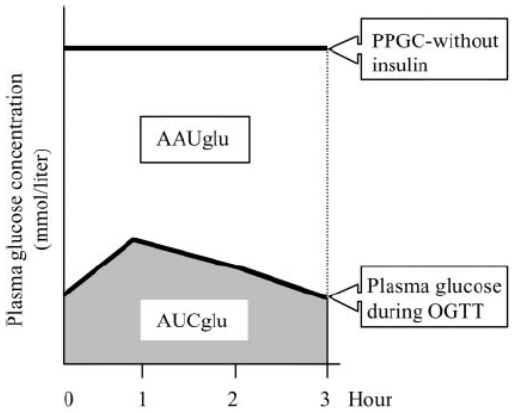


Figure 6 The model derived for calculating insulin sensitivity index using area under curve method [13].

Because the indexes in steady state group use only the fasting glucose and insulin level, these models cannot represent the complex interaction between glucose and insulin in postprandial state, the state after meal ingestion which is the major disadvantage of these methods. Subjects with small insulin deficiency, the fasting blood glucose values does not show the problem. A heavy glucose load into the system is required to reveal the abnormality of the glucose-insulin interaction [14].

2.2 Dynamic intervention methods

Since the homeostasis state may not reveal a real problem of glucose-insulin interaction, perturbing the system and observe the response become an interesting method. The method in this group monitors the dynamic response of the glucose-insulin system when the system is challenged by glucose load either by direct injection into the blood stream or by ingestion. The methods in this group are glucose clamp, intravenous glucose tolerance test and oral glucose tolerance test.

2.2.1 Hyperinsulinemic euglycemic glucose clamp

Hyperinsulinemic euglycemic glucose clamp [15] is performed by acutely raising plasma insulin concentration to the high level and maintains it in order to maximize the glucose uptake by skeletal muscle. It is assumed that the suprabasal level of insulin shuts down endogenous insulin production by pancreas and shuts down endogenous glucose production by liver. During the hyperinsulenemic infusion,

the external glucose is infused continuously to maintain the patient's fasting glucose concentration. The rate of glucose infusion implies the rate of glucose disappearance from the blood. The insulin sensitivity can be calculated from

$$\textit{insulin sensitivity index} = \frac{\text{the rate of glucose uptake [mg/kg/min]}}{\text{unit insulin concentration [}\mu\text{U/ml]}} \quad (4)$$

Clamp technique is referred to as the gold standard in measuring insulin sensitivity. The disadvantages of clamp technique are that infusing a high level of insulin is not a normal physiology of the body and it interferes with the endogenous insulin production. For this reason, clamp technique is not suitable for testing some new therapies concerned with the insulin production from pancreas.

2.2.2 Glucose tolerance test

The idea of the glucose tolerance test is to challenge the homeostasis mechanism by a dose of glucose. It is assumed that "the subsequent rise and fall of the blood glucose is due mainly to production of insulin in response to hyperglycemia and that the degree of insulin response is mirrored in the behavior of the blood glucose" [14]. If the glucose load is injected intravenously, It is called the intravenous glucose tolerance test (IVGTT). Another approach is called oral glucose tolerance test (OGTT) where a glucose dose is administered orally.

In intravenous glucose tolerance test, the subject is administered the known dose of glucose into the circulation which simplifies the circulation by the fact that the plasma glucose concentration is perturbed by the known dose of external glucose input. The disadvantage of IVGTT is that perturbing the system by injecting a bolus of glucose in the bloodstream does not represent the real glucose-insulin system in human body. It is also found that the insulin response to the increasing blood glucose from glucose injected intravenously is lower than from orally ingested glucose because the injection modifies the late phase of endogenous insulin secretion.

Oral glucose tolerance test or meal glucose tolerance test is a method that can quantify insulin sensitivity under normal life condition. It is also suitable for epidemiological studies because the procedure is simple and cheap.

Clinically, the criteria for interpretation of the glucose tolerance test are based on the glucose concentration level at several time points but do not take the insulin into account. It cannot determine whether the glucose disappearance is due to the insulin sensitivity or the glucose-induced insulin response. To solve this problem, the mathematical model has been used to describe the system of glucose-insulin interaction. The widely used model for glucose insulin kinetics is called the Minimal Model developed by Bergman et. al. in 1979 [2].

3. The Minimal Model for Glucose Kinetics

The minimal model is based on the physiological regulation scheme shown in Figure 7. The system consists of a glucose compartment (g) and remote insulin compartment which control the glucose flux. Glucose concentration in glucose compartments comes from the external glucose, $R_a(t)$ (glucose injection for IVGTT or glucose absorption from oral intake for OGTT) and hepatic glucose. Parameter k_5 represents the net hepatic glucose balance (NHGB) which is the net rate of glucose uptake and glucose production from liver. Hepatic glucose rate is controlled by k_6 which is the net rate of effect of insulin on glucose uptake and production in liver. k_1 is the rate of glucose uptake by body tissue via diffusion and GLUT-4 at basal insulin-level. k_4 is the rate of GLUT-4 facilitated diffusion per unit of insulin concentration. k_3 is the constant loss rate of remote insulin degradation. k_2 is the insulin transport rate from plasma-insulin to extracellular fluids. The parameters in this physiological scheme are reduced to yield the minimal model shown in Figure 8.

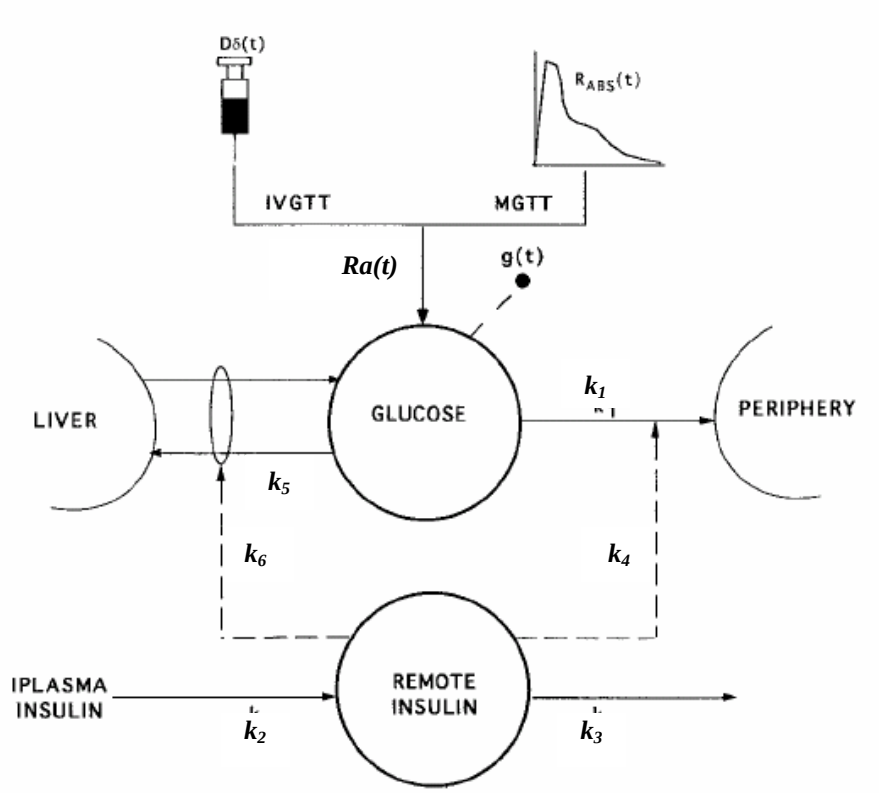


Figure 7 The physiological regulation used to interpret the IVGTT test [16]

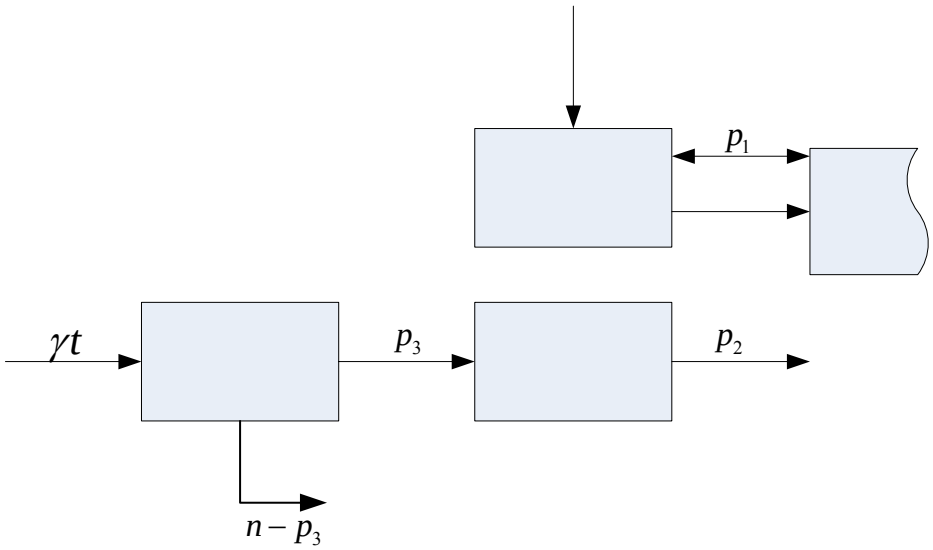


Figure 8 The minimal model for glucose kinetics

The differential equations and parameters' description of the minimal model are as follows:

$$\frac{dG(t)}{dt} = -p_1\left[G(t) - G_b\right] - X(t)G(t) + R_a(t) \quad G(0) = G_b \tag{5}$$

$$\frac{dX(t)}{dt} = p_3\left[I(t) - I_b\right] - p_2 X(t) \tag{6}$$

$$\frac{dI(t)}{dt} = \gamma\left[G(t) - h\right]t - nI(t) \tag{7}$$

$$S_G = p_1 \tag{8}$$

$$S_I = \frac{p_3}{p_2} \tag{9}$$

where G(t) is plasma glucose concentration at time t [mg/dl]

I(t) is plasma insulin concentration at time t [μU/ml]

X(t) is the remote insulin in action which effects the net glucose appearance [min^{-1}]

$R_a(t)$ is the rate of glucose appearance in the blood [mg/dl]

p_1 is the rate of insulin-independent glucose disappearance [min^{-1}]

p_2 is the constant loss rate of remote insulin degradation [min^{-1}]

p_3 is insulin-dependent increase in tissue glucose uptake ability per unit of insulin concentration above the baseline insulin [$min^{-2}(\mu U/ml)^{-1}$]

n is the first order decay rate for plasma insulin [min^{-1}]

h is the threshold value for plasma glucose above which the pancreatic β-cell release insulin [mg/dl]

γ is the rate of endogenous insulin secretion with glucose concentration above h [$(\mu U/ml)min^{-2}(mg/dl)^{-1}$]

G_b is baseline plasma glucose [mg/dl]

I_b is baseline plasma insulin [μU/ml]

S_G is glucose effectiveness [min^{-1}]

S_I is insulin sensitivity [$\min^{-1}(\mu U/ml)^{-1}$].

4. Rate of Glucose Absorption from Oral Glucose Tolerance Test

The main problem in applying the minimal model to OGTT is that the input of the system, the rate of glucose appearance in circulation, is not known. Many works have been focused on solving this limitation. This section shows some works on modeling the input of the oral glucose minimal model.

Tracers have been used in many researches in order to investigate the glucose and insulin kinetics. Tracers are substances administered into the system to estimate the quantitative information of events characterizing the kinetics of the substance [17]. The common model to calculate glucose kinetics is the Steele's single pool model proposed by Steele et. al. [18]. This model assumed the body as a single pool consists of glucose in aqueous solution in a well-stirred space of constant volume, V. The gradient distribution of glucose in a single pool is introduced as a rapidly mixing fraction, p, of the total volume.

A dual tracer OGTT with Steele's single pool model and a new oral minimal model is presented by Zijlstra [3]. This approach used the rate of appearance of orally ingested glucose, Ra gut(t), estimated from Steele's model as an input to the oral minimal model. Figure 9 shows the diagram of this approach.

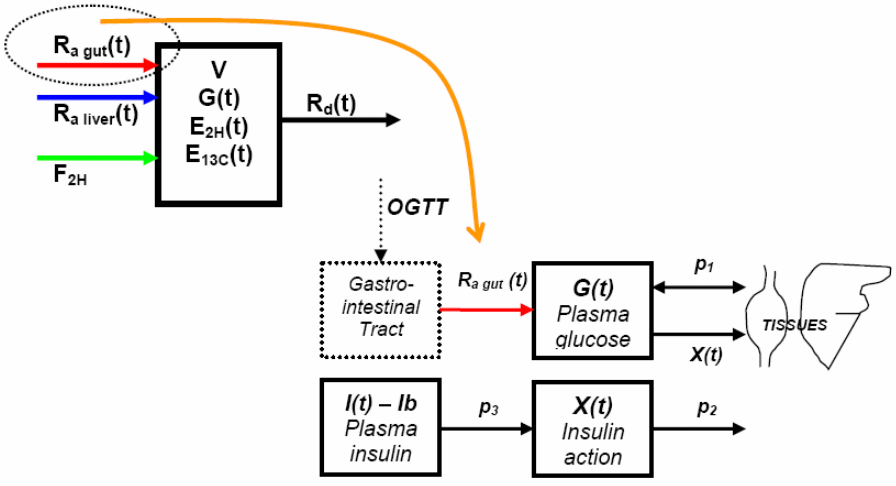


Figure 9 The oral minimal model in combination with Steele's estimation of gut-glucose appearance as an input proposed by Zijlstra.

The dual tracer method enabled simultaneous in vivo measurement of both the systemic rate of appearance of the ingested glucose and postprandial endogenous glucose production (EGP). This method utilizes two tracers to distinguish between the glucose fluxes from the gut and from the liver. The first tracer is infused intravenously ([6,6-$^{2}H_2$] glucose) to measure the rates of appearance of the ingested and total glucose (R_a).The second tracer ([U-^{13}C] glucose) is in the ingested glucose to enable tracing the rate of appearance from gut-glucose. The fraction of total glucose appearance from gut is given by;

$$R_{a\,gut}(t) = \frac{E_{13C}(t)}{E_{bolus}} R_a(t) \tag{10}$$

where $R_{a\,gut}(t)$ is the rate of appearance of orally ingested glucose

$E_{13C}(t)$ is [U-^{13}C]glucose enrichment

E_{bolus} is [U-^{13}C]glucose enrichment of the oral bolus.

Tracer method is a common method to investigate glucose kinetics. However, the procedure is quite complex and uncomfortable to subject. Several studies have therefore been focused on a non-tracer method. Parametric model is one of interesting approaches.

Natalucci et. al. [19] proposed the one compartmental model of the conversion of food into the rate of glucose appearance in plasma, Ra. The glucose appearance model is coupled with the classical minimal model. The model of Ra is;

$$\frac{dG_{gut}(t)}{dt} = R_{ge}(t) - k_{abs} \cdot G_{gut}(t); \qquad G_{gut}(0) = 0 \tag{11}$$

where $G_{gut}(t)$ is glucose mass in gut

k_{abs} is the rate constant of glucose absorption from the gut to the systemic absorption

$R_{ge}(t)$ is the rate of gastric emptying which provides the glucose flux into the small intestine. The gastric emptying is an exponential function [20].

Di Nardo et. al. [21] proposed the gut model developed from Natalucci's model. The new model supposed that the ingested glucose dose, D is converted into the rate of post hepatic glucose appearance into plasma $R_a(t)$. The glucose input of gut compartment comes from stomach governed by the gastric emptying function. The rate of glucose delivered by the gut consists of two parts; the post hepatic appearance of ingested glucose into the systemic circulation and the splanchnic extraction (liver and small intestine). The equation of gut compartment of this new model is

$$\frac{dG_g(t)}{dt} = R_s(t) - \left[R_a(t) - r_l(t)\right] = R_s(t) - k_d G_g(t); \qquad G_g(0) = 0 \tag{12}$$

$$R_s(t) = D \cdot \ln 2 \cdot 2^{-\left[(t-t_i)/\tau\right]^{\beta}} \cdot \frac{\beta}{\tau}\left[\frac{t+t_i}{\tau}\right]^{\beta-1}; \; 0 \le t \le 300\,\text{min} \tag{13}$$

where $G_g(t)$ is glucose mass in gut (*mg*)

$R_l(t)$ is the rate of splanchnic extraction of glucose (*mg/min*)

$R_a(t)$ is the rate of post hepatic appearance of ingested glucose into the systemic circulation (*mg/min*)

$R_s(t)$ is the rate of glucose flow from stomach into the gut compartment (*mg/min*)

ß is the gastric retention decay parameter

τ is the time lasting until 50% of glucose dose D has been delivered (*min*)

k_d is the delivery constant.

The rate of glucose delivery is assumed to be linearly related to the glucose mass in the gut. Therefore, the rate of appearance of ingested glucose into plasma is

$$R_a(t) = k_{abs} \cdot G_g(t) \tag{14}$$

$$k_{abs} = f \cdot k_d \tag{15}$$

where f is the fraction of glucose delivered by the gut.

5. The Minimal Model with Reduced Sampling Schedule

In 1991, Cobelli et. al. proposed the sampling schedule for glucose and insulin concentrations with a reduced number of samples by designing in the optimal way [22]. The optimal sampling schedule is defined as the schedule which the maximal precision of the model parameter estimates is achieved. The IVGTT experiment was performed in ten normal subjects. The schedule for glucose and insulin concentration was first computed separately. Then the common sampling schedule was computed. They concluded that the suitable sampling schedule is 14 samples. The time interval 10-40 min is the maximal informative for the estimation parameters. However, they commented that the experiment should be further performed in pathological subjects.
In 1993, Steil et. al. proposed the new sample schedule for IVGTT that minimizes the variance of the parameter estimates and the error in reconstructing the plasma insulin profile [23]. The reduced schedule consisted of 12 samples. Eighty-seven subjects performed IVGTT. The data were used to estimate parameter from reduced sampling schedule (RSS) compared with full scale schedule. They concluded that the result in normal subject was better than in NIDDM patients. Coates et. al. suggested that the 13 samples schedule yielded the better result than 12 samples [24]. Their proposed schedule seemed to be appropriate for both normal subjects and NIDDM patients. In 1996, Nguyen et. al.[25] proposed a new 13-sampling schedule developed from Steil. The new method provides better correlation and lower bias in the estimation of both insulin sensitivity and glucose effectiveness in both normal subjects and NIDDM patients. In 2005, Dalla Man et. al. proposed a two-hour seven-sample protocol for oral and meal glucose tolerance test [26]. They examined the insulin action and β-cell function (measuring insulin secretion) using the glucose and C-peptide oral minimal model. The protocol applied the rate of glucose appearance model as an input into the oral glucose minimal model. The reduced protocol consists of 7 samples within the first 2 hours after glucose or mixed meal ingestion. The insulin sensitivity index and the β-cell function index from the reduced protocol are compared with the references value which is calculated from the full protocol. They concluded that the reduced protocol could estimate both insulin secretion and insulin action accurately.

6. Reduced Sampling Schedule Optimization

In designing reduced sampling schedule (RSS) it is important to determine which sampling points should be assigned in the reduced schedule. To create RSS consisting of 10 samples during 0 to 300 minutes of oral glucose tolerance test, for example, there are more than 10^{300} possible ways to arrange sampling schedule. Finding suitable sampling schedule is a combinatorial optimization problem, the problem of finding the configuration of parameters $X=[x_1,x_2,...,x_m]$ in discrete solution space that minimizes objective function f(X). This type of problem can be solved by several heuristic search methods such as genetic algorithm, tabu search and simulated annealing (SA) algorithm.

Iterative improvement strategies or hill climbing method is the basic optimization algorithm. The idea can be imagined as releasing the ball from the top of the hill. The ball will roll downhill and trap in the nearest minimum point. In the same manner, the process of optimization start with the initial random configuration, then the iterative improvement algorithm explores the neighboring configurations and moves to one with the most improvement, in the other word, one that has the least objective function value. The algorithm is stopped if there is no further improvement. The disadvantage of this strategy is that the solution is trapped in the nearest local minima because it always moves downhill. Global minima solution may be discovered only if the algorithm starts close to it. SA algorithm overcomes these problems by allowing next configuration to move uphill with some controlled probability, giving a chance of jumping out of local minima.

Simulated annealing algorithm is analogy to the mechanical annealing used in hardening glass and metal. The annealing process consists of two steps; increase the heat to the maximum value at which the material melts and then carefully decrease the temperature until the atoms of material are arranged in the ground state. At high temperature the atoms can move freely through states of higher energy. At each lowered temperature, the metal reaches the global minimum energy state, the atoms lose the mobility and lie in the most stable orientation and form a pure crystal. If a

melted metal is cooled too fast, the metal might not escape from a local minimum energy and will end up in a polycrystalline or amorphous state.

In 1953, Metropolis [27] proposed the algorithm to simulate the evolution of a solid in a heat bath to thermal equilibrium based on Monte Carlo technique. The algorithm begins with setting initial configuration, i, and randomly selects new configuration, j. Each configuration has its own energy which is defined by the objective function. The difference of energy between current and new configuration, $\Delta E = E_j - E_i$, is evaluated. the Metropolis Monte Carlo algorithm chooses new configuration with probability $e^{\left(\frac{-\Delta E}{kT}\right)}$. If the new configuration has lower energy than current configuration or $\Delta E < 0$, it is always accepted as the new starting point of the next selection. If the new configuration is worse, it may be acceptable with a probability that depends on the energy difference and current temperature as followed;

$$P\{accept\} = \begin{cases} 1 & if\ \ \Delta E \le 0 \\ e^{-\left(\frac{\Delta E}{T}\right)} & if\ \ \Delta E > 0 \end{cases} \tag{16}$$

where P is acceptance probability T is the control parameter analogy to temperature in mechanical annealing. Accepting worse configuration allows the search algorithm to jump out of the local minima. This acceptance rule is known as Metropolis criterion.

Metropolis algorithm is applied to optimization problem in 1982 by Kirkpatrick [28] and named as Simulated Annealing. SA algorithm consists of two nested DO-loops. The outer-most loop is the decrement of the temperature, from the high initial temperature to the low final temperature. This loop is called the cooling schedule. The inner-most loop is a Metropolis Monte Carlo simulation which iterates over the specific number of Monte Carlo attempts.

SA algorithm starts with high temperature. At this temperature, a large number of worse configurations will be accepted. As temperature decreases only a few of them will be accepted. The algorithm then moves downhill only, similar to the hill climbing method. Probability of accepting bad move is implemented by comparing acceptance probability with a random number generated from a uniform distribution on the

interval [0, 1). When the Metropolis iteration loop is done, the temperature is reduced to the next level and the Metropolis loop is evaluated again. This process is repeated until the stopping criterion is met.

Two key factors of SA algorithm are cooling schedule (the way to decrease temperature) and energy (cost of objective function). Cooling schedule is the factor that moderates the acceptance of solution. Among many available cooling schedule, the proportional cooling schedule, $T_{new} = \alpha T_{old}$ where $\alpha < 1.0$, is often used. Energy in SA is equivalent to objective function value calculated from objective function. The goal of SA is similar to mechanical annealing which aims at finding the configuration of parameters (analogy to arrangement of atomic particle) that minimizes the objective function value of the problem (analogy to the energy of the system).

7. Summary

Insulin sensitivity index is a useful tool for diagnosing deficiency in blood glucose regulation system, especially diabetes. Various methods of estimating insulin sensitivity are available nowadays but there is a trade-off between information and number of samples. Indexes in homeostasis method group need only a few numbers of samples which make the methods cheap and simple, but the information is only accounted for the glucose and insulin level in steady state. While the index from dynamic intervention group can explain how the body responses to an external dose of glucose, many sample data are nevertheless needed. Consequently, the test is expensive, difficult and time consuming. The method with fewer data points yet give informative interpretation of body response will increase the efficiency of diagnosis and with the reasonable cost of the test. The method will be able to be used clinically in the future. This research focuses on reducing the samples needed for the oral glucose minimal model. The oral minimal model previously described in section 3 is coupled with the model of glucose absorption selected from section 4.The details of algorithm used for finding optimal sampling schedule and the experimental methodology are described in the next chapter.

CHAPTER III
MATERIALS AND METHODS

The experiment of this study was based on computer simulation since the real experiment in human is difficult and expensive. The study focuses on Normal Glucose Tolerance (NGT) subject because parameter values and experimental data of NGT data are available in many research articles [19, 26, 29-31]. Parameter values of IGT and DM subject were rarely available because failure of parameter fitting often occurred. The experiment of IGT and DM subject was then excluded from this study. The glucose and insulin profile of NGT subject were generated from the insulin kinetics model and the oral minimal model proposed by Di Nardo [21] described in chapter II section 4. This model was chosen because it is simple yet close to physiological system. It is considered that a part of the glucose delivered by gut is extracted and utilized by liver and intestine. Only a fraction of glucose is absorbed into blood circulation. The rate of glucose absorption simulated from the oral minimal model is shown in Figure 10. This absorption model is coupled with classical minimal model and is called "the oral minimal model" later on in this thesis. The oral minimal model is described as

$$\frac{dG(t)}{dt} = -p_1\left[G(t)-G_b\right] - X(t)G(t) + \frac{R_a(t)}{VW} \quad , G(0) = G_b \tag{17}$$

$$\frac{dX(t)}{dt} = p_3\left[I(t)-I_b\right] - p_2 X(t) \quad , X(0) = 0 \tag{18}$$

$$\frac{dG_g(t)}{dt} = R_s(t) - \left[R_a(t) - r_l(t)\right] = R_s(t) - k_d G_g(t) \quad , G_g(0) = 0 \tag{19}$$

$$\frac{dI(t)}{dt} = \gamma\left[G(t)-h\right]t - nI(t) \quad , I(0) = I_b \tag{20}$$

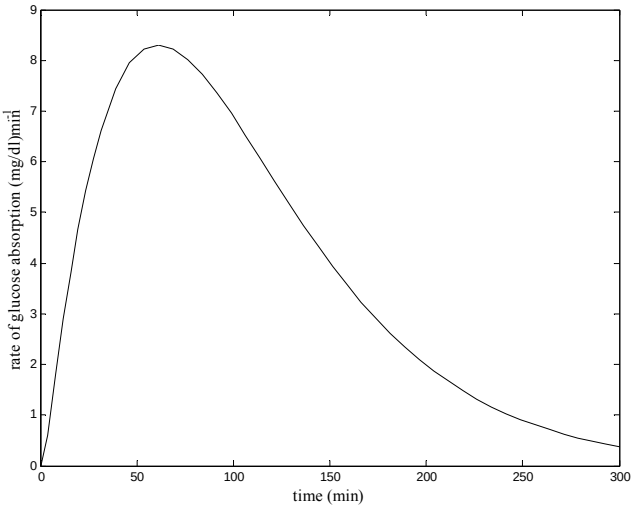


Figure 10 Rate of glucose absorption simulated from the oral minimal model.

VW is glucose distribution volume (*dl*). The definition of other parameters and variables in the oral minimal model were described in Chapter II sections 3 and 4. The diagram of oral minimal model and glucose absorption model are illustrated in Figure 11 and 12Figure 12, respectively.

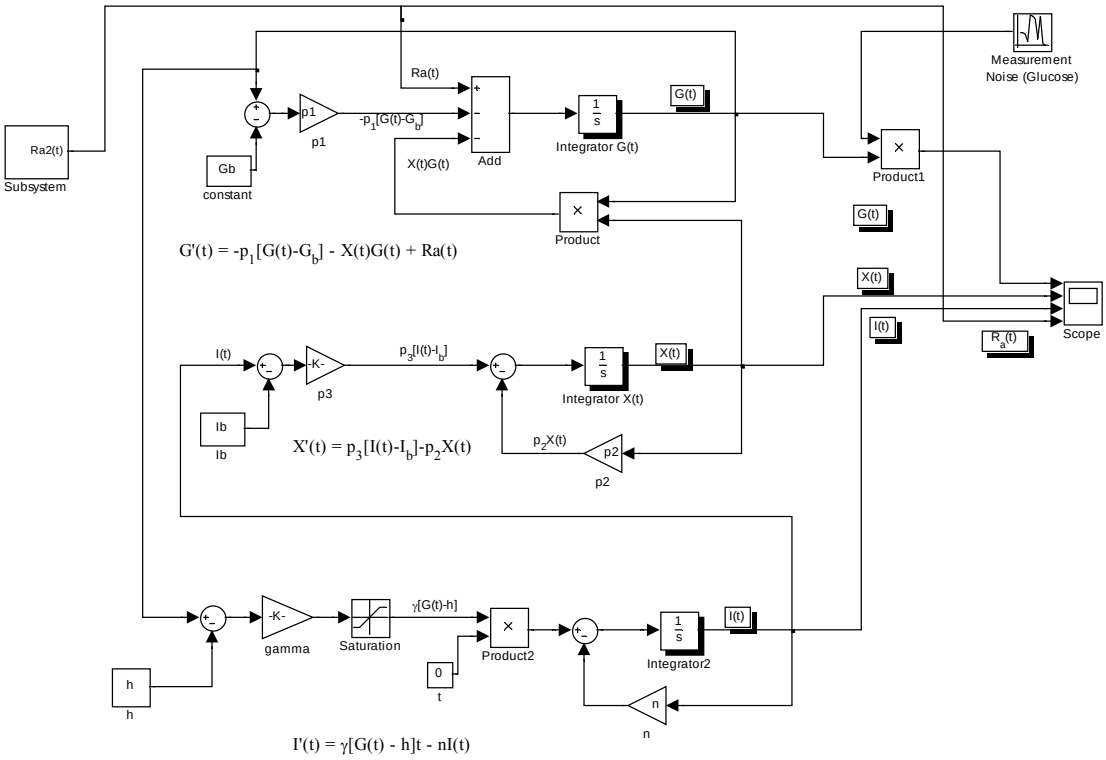


Figure 11 Diagram of the oral minimal model

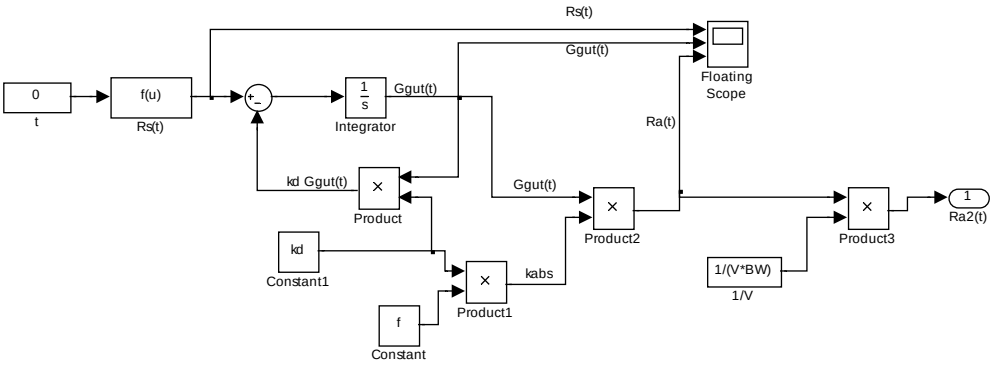


Figure 12 Diagram of glucose absorption model

Parameter values for generating NGT data were summarized from several researches [3, 21, 30, 32]. The parameter values varies within the following ranges: $p_1 \in [1.4\ 3.1]\cdot 10^{-2}\,\mathrm{min}^{-1}$, $p_2 \in [1.1\ 2.5]\cdot 10^{-2}\,\mathrm{min}^{-1}$, $S_I \in [7.1\ 12.3]\cdot 10^{-4}\,\mathrm{min}^{-2}\left(\mu U/ml\right)^{-1}$. Parameters for insulin kinetics in Eq.20 are taken from [33] where $\gamma = 0.0033\left(\mu U/ml\right)\left(mg/dl\right)^{-1}\left(\mathrm{min}^{-2}\right)$, $n = 0.3\mathrm{min}^{-1}$,and $h = 90\,mg/dl$. The data was simulated at every 1 min, from 0 to 300 min and was defined as the full sampling schedule data (FSS). Figure 13 shows the simulated data of NGT. The bold line represents the average value of glucose concentration. The upper and lower bound of the concentration are represented by the thin lines.

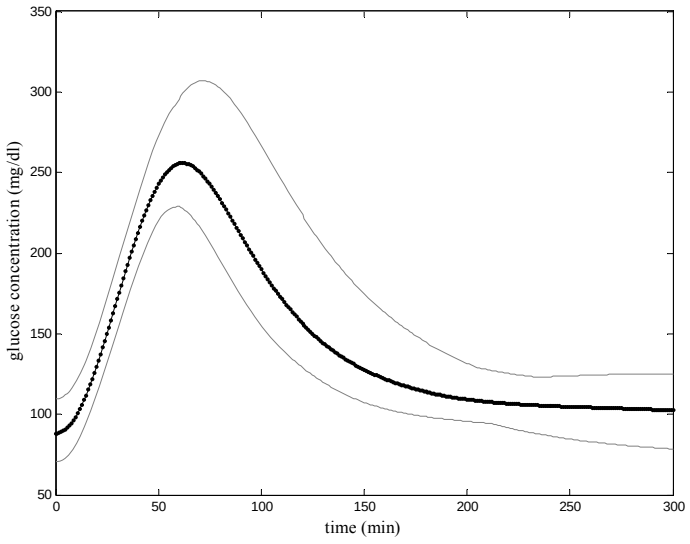


Figure 13 Simulated glucose profiles of NGT data

The Insulin sensitivity index was estimated by the nonlinear least squares algorithm as implemented on MATLAB© (Mathworks Inc., USA). Further description of parameter estimation is described in the next section. The insulin sensitivity index computed from FSS (s_I^{FSS}) was used as a reference value. The reduced sampling schedule (RSS) which consisted of 30, 25, 20, 15, 10, 9, 8, 7, 6 and 5 samples were evaluated by simulated annealing (SA) algorithm. Additional details of evaluating RSS are described in section 2. The maximum number of sample taken in RSS was set at 30 samples because it is a common number of samples taken in real experiment involved with minimal model. The subsequence sections gave details about two major components in this study; the method of estimating S_I and the method of selecting reduced sampling schedule with predefined number of samples. The last section describes the methodology of obtaining optimal sampling schedule for oral glucose tolerance test data. The diagram of overall procedure of this study is shown in Figure 14.

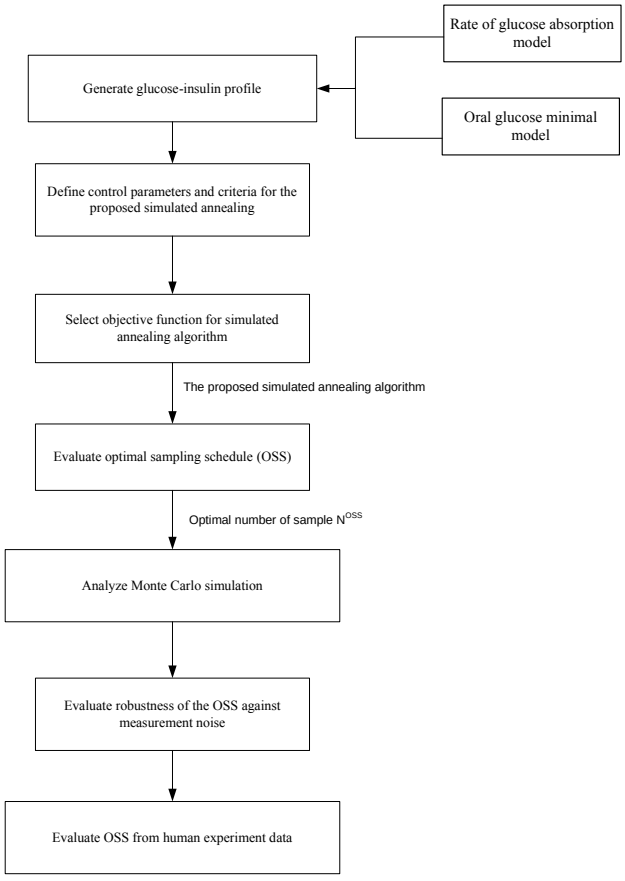


Figure 14 The overall procedure of the research work

1. Insulin Sensitivity Index Estimation

Parameter estimation utilized the minimization function available in optimization toolbox of MATLAB. The parameter was identified by the Levenberg-Marquardt nonlinear least square method. The process of parameter identification begins with initializing the parameter values in minimal model, p_1 p_2 and p_3.The insulin profile is inputted to the model to obtain the predicted glucose profile. The criterion function value, defined as the sum of square error between glucose concentration from experiment, and concentration predicted from model are computed by Eq. 21. The algorithm search for a parameter set that minimizes value of the criterion function. S_I is computed from these parameter values. Figure 15 depicts the process of parameter estimation.

$$J = \sum \left[G_{\text{experiment}} - \hat{G}_{\text{predicted}} \right]^2 \tag{21}$$

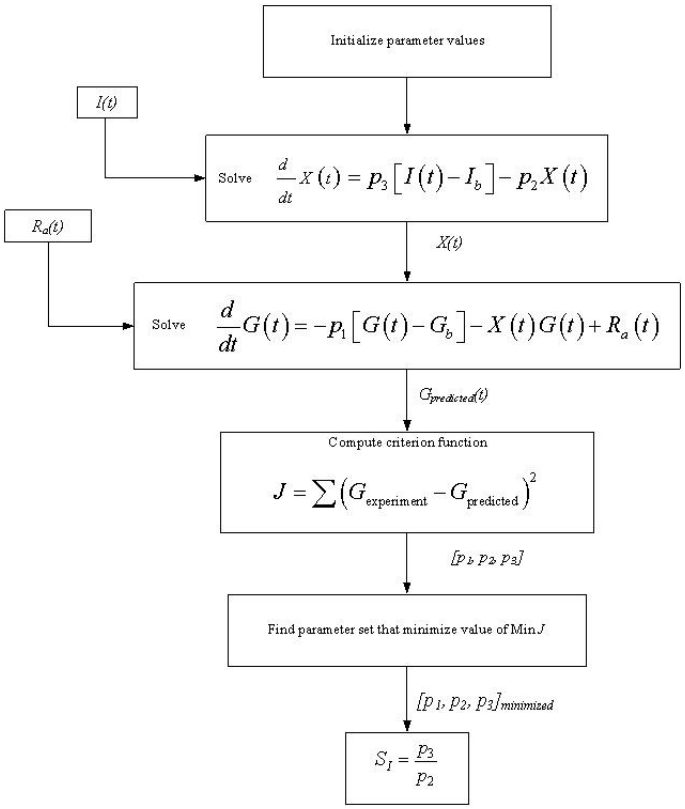


Figure 15 Parameter estimation process (modified from [34])

2. Selecting Reduced Sampling Schedule by Simulated Annealing

In order to find the suitable arrangement (or configuration) for each RSS, the SA method is employed. The proposed SA method implemented in this study is adapted from [35]. The diagram of the proposed algorithm is depicted in Figure 16. The details are described as follows:

1. Set the initial temperature, T, and the number of Metropolis Monte Carlo simulation at each temperature, L.
2. Set the initial reduced sampling schedule of m samples, $t=(t_1, ..., t_m)$.
3. Generate the new sampling schedule, t_{new}. Further detail is described in section. 2.1.
4. Calculate energy of the current schedule ($E_{current}$) and the new schedule (E_{new}) from objective function described in section 2.2.
5. Check whether the new schedule should be accepted or not using acceptance criterion as stated in Eq. 16.
   - If the new schedule has lower energy than the current schedule, it is always accepted. Replace the current schedule with new schedule.
   - If the new schedule has higher energy, the acceptance probability of the new sampling schedule is computed. If the probability is higher that random number r, where $r \in [0,1)$, the new schedule is accepted.
6. Repeat steps 3 to 5 for L times.
7. Calculate the next temperature from cooling schedule, $T_{new} = \alpha T_{current}$, where α is a constant.
8. Repeat the whole process until the stopping criteria is met. More detail on stopping criteria is described in section 2.3.

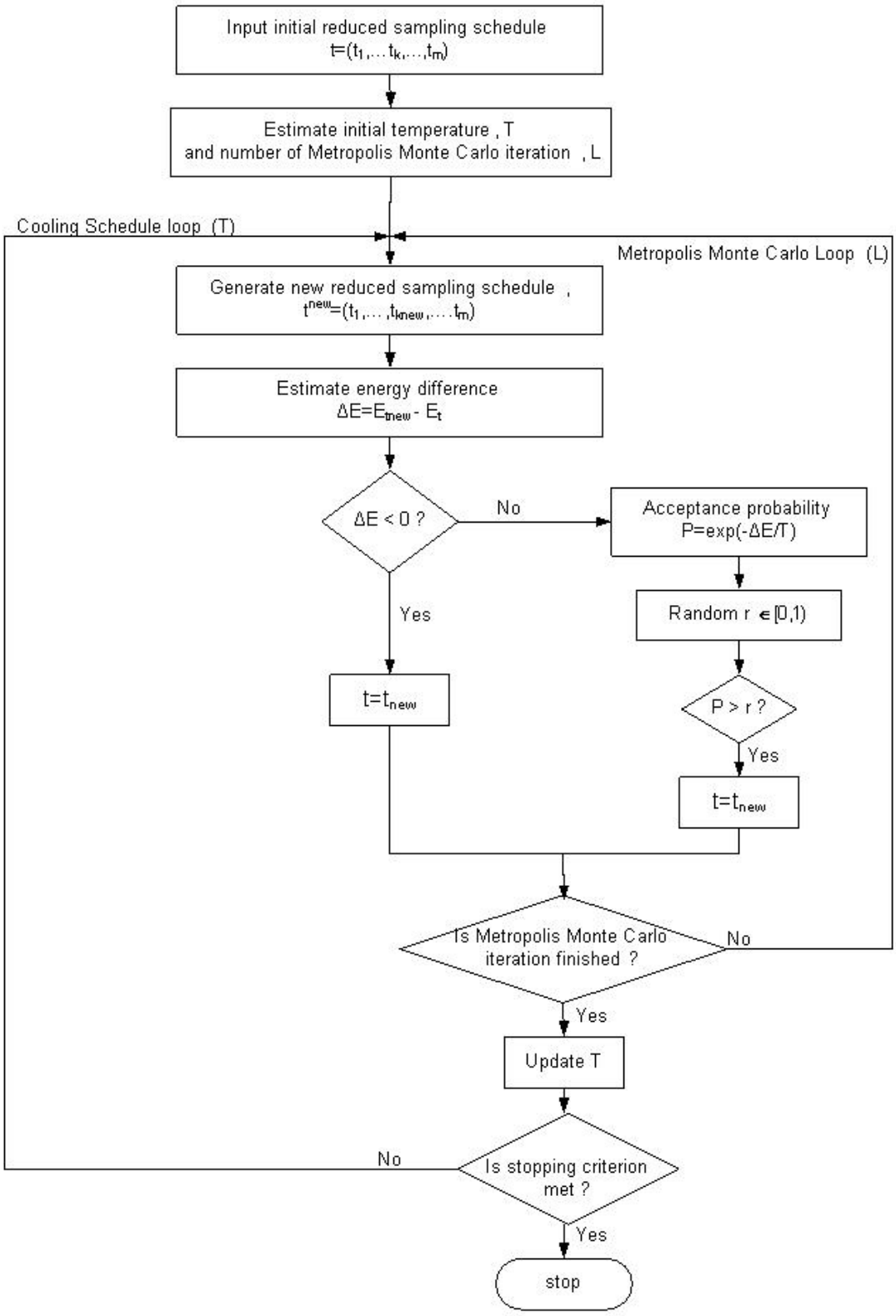


Figure 16 The SA algorithms for selecting reduced sampling schedule

2.1 Generating new sampling schedule

Let $t=(t_1, t_2, ..., t_m)$ be a sampling schedule. The process of generating new sampling schedule starts by randomly selected a sampling point t_k from $t_1,\ldots,t_m$ as shown in Figure 17a. Next, the new sampling point, t_{knew}, is selected from the sampling point between t_{k-1} and t_{k+1}. The sampling point t_k is replaced by t_{knew} as shown in Figure 17b.

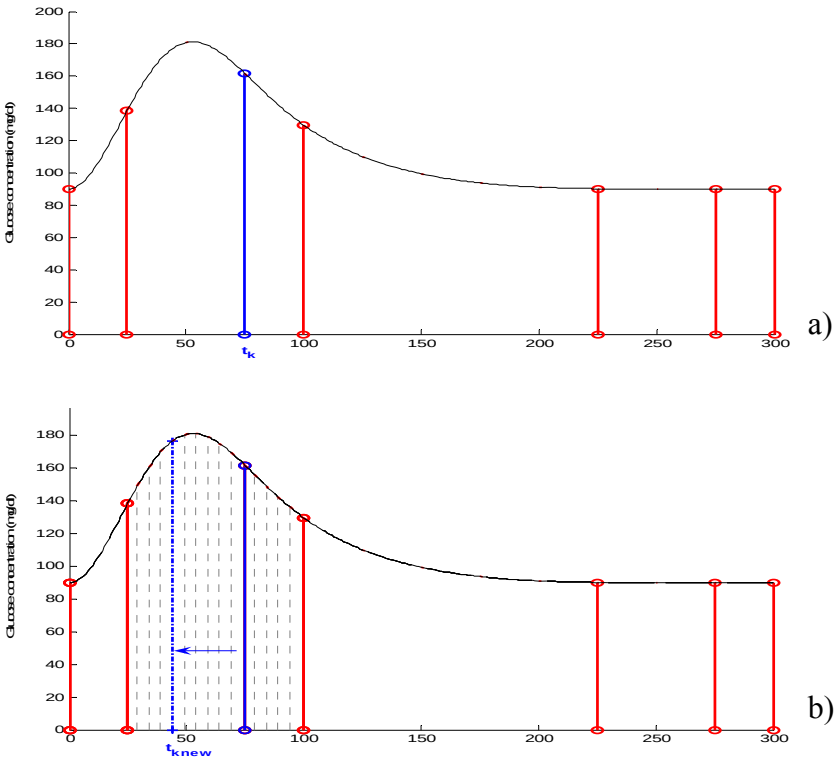


Figure 17 Process of generating new sampling schedule a) randomly select t_k from current schedule $t_{current}=t_1,\ldots t_k\ldots, t_m$. b) replace t_k with t_{knew}. The new schedule is $t_{newt}=t_1,\ldots t_{knew}\ldots, t_m$

2.2 The objective function

The objective function is evaluated to measure the quality of each sampling schedule. The proposed objective function is based on the mean squared error of glucose concentration, estimated by using linear interpolation approximation. The linear interpolation of glucose concentration, $\widehat{g}_i(t)$, from t_i to t_{i+1} is given by

$$\widehat{g}_i(t)=a_i t+b_i \quad for\, t_i \le t \le t_{i+1} \tag{22}$$

where $a_i = \frac{g_{i+1} - g_i}{t_{i+1} - t_i}$, $b_i = \frac{g_i t_{i+1} - g_{i+1} t_i}{t_{i+1} - t_i}$.

The mean squared error between FSS glucose concentration, G(t), and estimated value from linear interpolation $\widehat{g}_i(t)$ is

$$MSE = \sum_{i=1}^{m-1} \int_{t_i}^{t_{i+1}} E\left\{\left[\widehat{g}_i(t) - G(t)\right]^2\right\} dt \tag{23}$$

Model parameters in oral glucose minimal model affect the glucose concentration in particular time intervals. Identifying which time interval gives most information on parameters is usually evaluated by using sensitivity analysis. This information is very useful in order to relate objective function to model parameters [36]. Sensitivity analysis of oral minimal model is evaluated by MATLAB function 'sense_sys' [37]. The sensitivity is obtained by differentiating the system of oral minimal model (21-23) with respect to p_1, p_2 and p_3 through a directional derivative finite difference approximation. Figure 17 shows time course of oral minimal model output with respect to parameters. It can be noted that p_1 is estimated in the interval 10 to 200 min, p_2 is estimated from 30 min to the end and p_3 is predominant in 40 min to the end. This information is used as a weight in linear interpolation. Suitable weight function for the OSS problem is selected from the experiment described in section 3.1. The objective function based on weighted mean squared error is

$$MSE = \sum_{i=1}^{m-1} \int_{t_i}^{t_{i+1}} w(t) \cdot E\left\{\left[\widehat{g}_i(t) - G(t)\right]^2\right\} dt \tag{24}$$

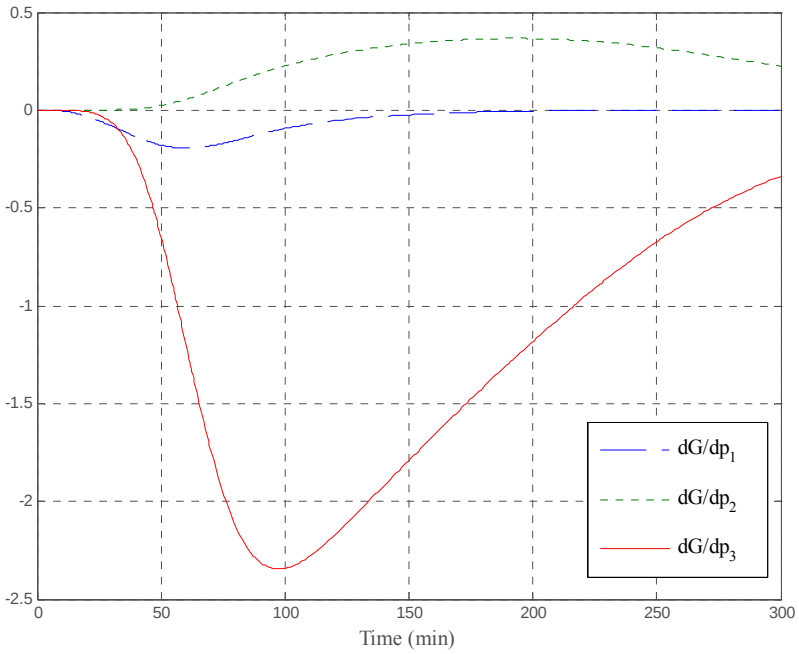


Figure 18 Model sensitivity with respect to model parameters of NGT subject

2.3 Cooling schedule

Cooling schedule consists of the method of decrementing the temperature and the criterion to terminate the algorithm or stopping criterion. Proportional cooling schedule with α between 0.8 and 0.99 is used to decrement the temperature. In case of stopping criterion, SA algorithm would be terminated when the energy of the last Metropolis Monte Carlo simulation iteration is insignificantly changed for a number of consecutive temperatures. The value of α together with the stopping criterion for SA algorithm used in this study will be selected by trial and error method. The method of choosing these control parameters is described in section 3.1.1.

3. Experimental Methodology

Sampling schedule with different numbers of samples was tested in order to find the reduced sampling schedule with least number of samples that stays within the accepted percentage error bound. The experiment consists of four parts. First, the suitable objective function and control parameters of the SA algorithm are selected. This proposed SA algorithm will be used throughout the rest of the experiment. Next,

the optimal number of sample together with its sampling schedule is evaluated. The selected OSS is then tested against measurement noise. The schedule selected by SA algorithm at each time point was analyzed. Finally, the OSS of human experiment data is evaluated.

3.1 Characteristics of the proposed SA algorithm

This experiment is to select the suitable control parameters for SA algorithm and to verify that the idea of weighting objective function as described previously gives better SA algorithm results for optimal sampling schedule problem. In this study, the efficiency of SA algorithm is referred to:

1. The ability of the SA algorithm to produce the RSS results in good estimation of S_I. Since the objective function of SA algorithm is not directly related to S_I as previously described in Section 3.2, the idea of weighting the error based on sensitivity of the model is expected to give better sampling schedule than SA algorithm without weighting. The method of selecting suitable objective function will be described in section 3.1.1.

2. SA algorithm is able to produce the best possible sampling schedule according to the objective function. This is a general characteristic of SA algorithm. This ability depends on the control parameter values of SA algorithm. Different numbers of samples in a schedule may require different control parameter values.

These two issues are thus evaluated to find the suitable condition of SA algorithm for optimal sampling schedule problem. The SA algorithm with suitable condition is called later as “the proposed SA algorithm” and would be used for the rest of the study. Three sets of NGT data will be used in this part of experiment. Further description of each issue is described in the following sections.

3.1.1. Objective function of the proposed SA algorithm

This part of experiment is to select the suitable objective function of SA algorithm. Four objective functions will be tested. These objective functions are based on mean squared error of linear interpolation estimation of glucose concentration and weighted with different weighing functions as follow:

1. the uniform weight (obj_u)

2. the normalized magnitude of glucose sensitivity with respect to p_1 (obj_p1)
3. the normalized magnitude of glucose sensitivity with respect to p_2 (obj_p2)
4. the normalized magnitude of glucose sensitivity with respect to p_3 (obj_p3).

RSS of three NGT data sets consisting of 5, 6, 7, 8, 9, 10, 15, 20, 25 and 30 samples will be evaluated by the SA algorithm with these four objective functions. The average percentage errors of S_1^{RSS} from all cases are then observed. The objective function that gives the best result will be chosen to be the objective function of the proposed SA algorithm.

3.1.2. Performance of SA algorithm

In the SA algorithm, numerous sampling schedules with different configurations are generated. Each sampling schedule has its own energy. Sampling schedule with minimum energy is called the best possible sampling schedule of the proposed SA algorithm.

For effective SA algorithm, the final sampling schedule should be the schedule with energy equals to the energy of the best possible sampling schedule. The efficiency of final solution can be evaluated by the performance error (ε) defined as

$$\varepsilon = \frac{E_{final} - E_{mn}}{E_{mn}} \times 100\% \tag{25}$$

where E_{final} is the final energy and E_{mn} is the minimum energy.

Three simulated NGT data are used to evaluate the efficiency of the proposed SA algorithm. Initially, the control parameter values for SA algorithm as suggested by [38-40] are fixed for every case of sample number. The suggested value are: Initial temperature = 1000, Cooling schedule = $T_{new}=0.9T_{current}$, Metropolis Monte Carlo iteration= 1000, and Stopping criterion= Energy of last trial of Metropolis Monte Carlo iteration changed less than 10 percent for 4 consecutive temperatures.

Next, RSS of 5, 6, 7, 8, 9, 10, 15, 20, 25 and 30 samples will be evaluated by the proposed SA algorithm from section 3.1.1. Performance error of each RSS is

observed. The control parameters were then calibrated by trial and error until the error less than 1 percent is obtained. The average performance error can thus be calculated. The suitable control parameters for each RSS will be used later on in this study.

3.2 Optimal number of sample and optimal sampling schedule of Simulated data

This experiment focused on simulated data without noise with assumption that these data were the true glucose concentration. The effects of measurement noise which often occurred in real experiment were ignored. RSS of NGT data was obtained from the proposed SA algorithm. RSS in this experiment consisted of 5, 6, 7, 8, 9, 10, 15 and 20, 25 and 30 samples. Mean of RSS, S_I^{RSS} and percentage error of each RSS were evaluated. RSS with percentage error less than 5 percent and with minimum number of sample was chosen to be the optimal number of sample, N^{OSS}, of the simulated NGT data.

3.3 Monte Carlo Simulation

Because the method in this study depends on the information of model parameter of individual, the OSS obtained from the proposed method is specific to each subject which is not practical for population utilization. This experiment aims to analyze the distribution of OSS in population. Thirty sets of NGT data were generated. OSS of each data set consisted of N^{OSS} samples, obtained from section 3.2, were evaluated. The objective function of simulated annealing was weighted by the sensitivity of each dataset itself. Each time point in sampling schedule, $t_1,...,t_{N^{OSS}}$, was statistically analyzed.

This experiment also tested the effect of noise on the OSS selected from the proposed algorithm. In real experiment, data is always corrupted by noise from instruments used in collecting and measuring blood sample. This measurement noise is usually assumed to be Gaussian. In this study, Gaussian noise with mean 0 and variance varied from 1 to 20 was added to glucose profile of 30 NGT data sets. The percentage error of S_I^{OSS} at each noise level was evaluated to observe the ability of OSS to recover the S_I from data with noise.

3.4 Validation of the reduced sampling schedule with human experiment data

This experiment validated the reliability of the RSS by performing the validation with three sets of human data. The glucose and insulin profile of OGTT data were taken from [26, 29]. Sampling schedule of subject 1, 2 and 3 consisted of 11, 19 and 22 samples, respectively Figure 19 shows the sampling schedule diagram of each subject. At each sampling time, plasma glucose and insulin concentrations were measured. Glucose and insulin profile of each subject are illustrated in Figure 20. S_I calculated from experimental sampling schedule was set as the S_I^{FSS}. Each data set was tested with mean RSS from section 3.2. The sample in RSS which was not available in experiment schedule was modified to the nearest available sample. The percentage error between S_I^{FSS} and S_I^{RSS} was compared.

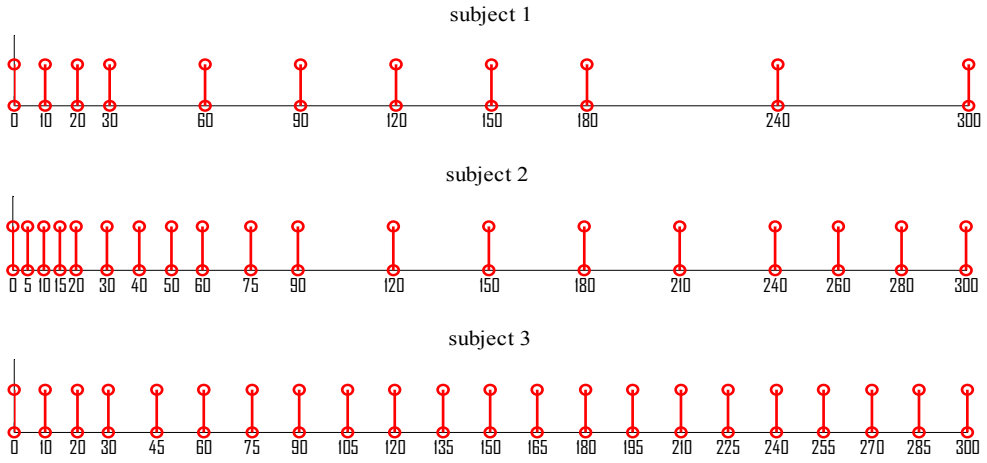


Figure 19 Sampling schedule diagram of 3 human experiment data sets

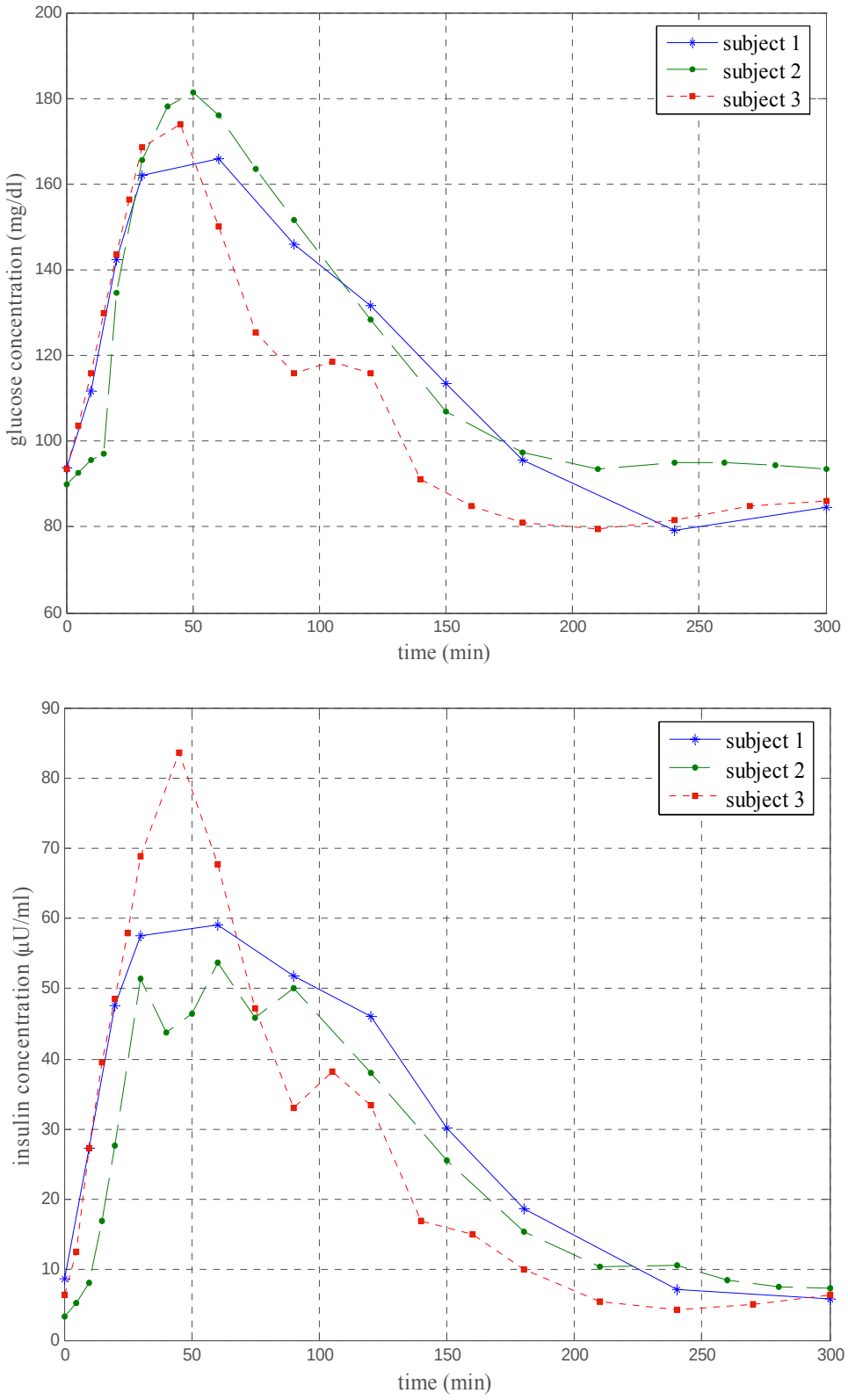


Figure 20 Glucose (upper panel) and insulin (lower panel) concentration from human experiment data

CHAPTER IV
EXPERIMENTAL RESULTS

This chapter reports the results from experiment described in previous chapter. The number of sample in sampling schedule in this study can be divided into 2 groups; the frequent sampling (15 samples or more) and reduced sampling (less than 15 samples). The suitable control parameters and objective function of the SA algorithm are determined from experiment in section 1. Section 2 reports the RSS and OSS for simulated data. Distribution of time point in OSS and robustness against noise are reported in section 3. Validation of RSS with human experiment data is reported in the final section.

1. Characteristics of the Proposed Simulated Annealing Algorithm

1.1 The Objective function of the proposed SA algorithm

The results of S_I^{RSS} estimated from RSS obtained from four objective functions SA algorithm are shown in Table 1**.** The average S_I^{FSS} is $12.007 \times 10^{-4}\text{min}^{-1}(\mu\text{U/ml})^{-1}$. Percentage error between S_I^{FSS} and S_I^{RSS} are shown in brackets and are plotted versus numbers of sample in Figure 21. RSS obtained from obj_p3 gives the best S_I^{RSS} estimation for all number of samples compared with other objective functions. In case of reduced sampling, obj_u produces highest estimation error. Percentage error of S_I^{RSS} converged when the number of sample in schedule is 15 or more. The range of S_I error from obj_u is between 1.02-24.71 percent, obj_p1 is between 2.67-22.91 percent, obj_p2 is between 1.04-14.42 percent, and obj_p3 is between 0.40-6.95 percent.

Table 1 S_I^{RSS} values estimated from RSS obtained from different objective function

Number of sample	S_I (10^{-4} min^{-1}(μU/ml)$^{-1}$)			
	obj_u	obj_p1	obj_p2	obj_p3
5	14.973 (24.71)	14.758 (22.91)	13.738 (14.42)	12.841 (6.95)
6	14.879 (23.92)	13.443 (11.96)	13.648 (3.67)	12.774 (6.39)
7	13.773 (14.70)	13.153 (9.54)	12.973 (8.04)	12.335 (2.73)
8	13.145 (9.48)	13.126 (9.32)	12.855 (7.06)	12.291 (2.37)
9	12.578 (4.75)	12.967 (8.00)	12.799 (6.60)	12.240 (1.94)
10	12.544 (4.48)	12.852 (7.04)	12.496 (4.08)	12.217 (1.75)
15	12.168 (1.34)	12.507 (4.16)	12.450 (3.69)	12.133 (1.05)
20	12.140 (1.10)	12.372 (3.04)	12.201 (1.61)	12.093 (0.72)
25	12.149 (1.18)	12.352 (2.87)	12.179 (1.43)	12.101 (0.78)
30	12.130 (1.02)	12.328 (2.67)	12.132 (1.04)	12.055 (0.40)

*Value in bracket is the percentage error compared with S_I^{FSS} of NGT data = 12.007×10^{-4} min^{-1}(μU/ml)$^{-1}$

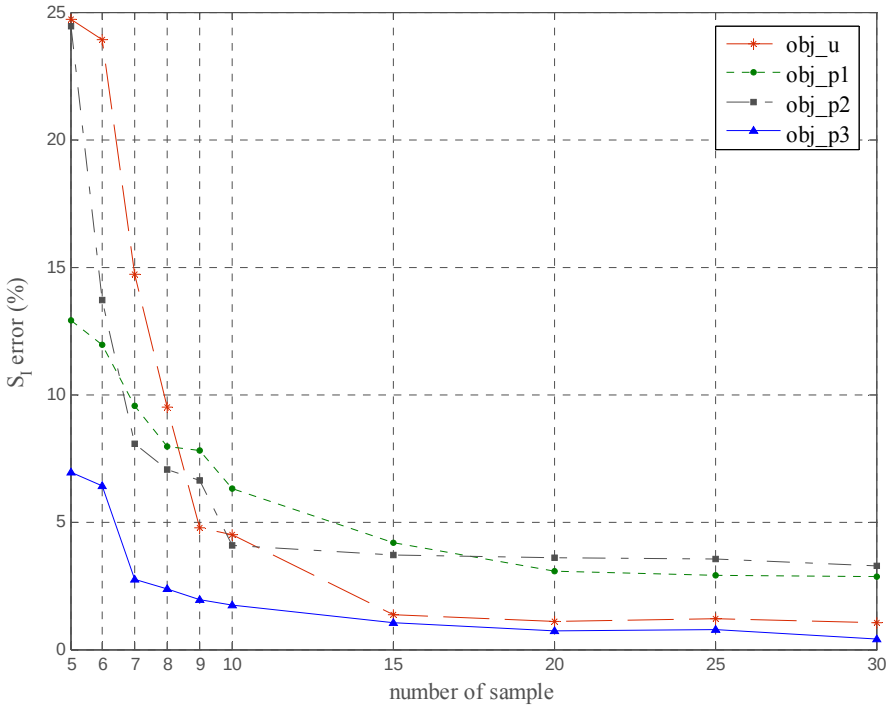


Figure 21 Percentage error of S_I^{RSS} obtained from different weight functions

1.2 Performance of SA algorithm

From the experiment described in section 3.1.2, the initial control parameter worked well for frequent sampling but not suitable for reduced sampling. The stopping criterion was adjusted from 4 consecutive temperatures to 6 consecutive temperatures in order to obtain better performance for all cases. The control parameter values for the proposed SA algorithm are shown in Table 2. Numbers of accepted schedule versus temperature and the energy versus iteration numbers are plotted in Figure 22.

Table 2. Control parameter for the proposed SA algorithm

Control parameter	**values**
Initial temperature	1000
Cooling schedule	$T_{new}=0.9T_{current}$
Metropolis Monte Carlo iteration	1000
Stopping criterion	Energy of last trial of Metropolis Monte Carlo iteration changed less than 10 percent for **6** consecutive temperatures

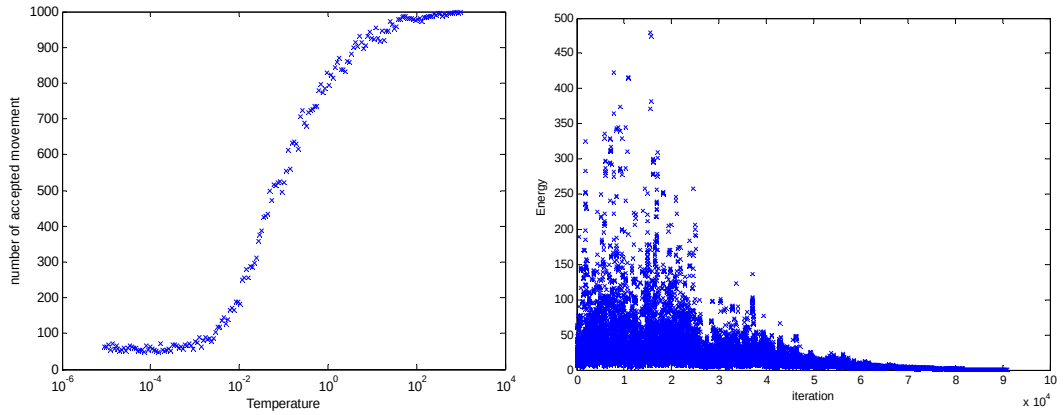


Figure 22 The number of accepted schedule at each temperature (left panel). The energy of accepted schedule as the number of iteration increase (right panel).

Performance of SA algorithm for each case is shown in Table 3. Figure 23 shows the comparison of minimum and final energy at each number of samples. The energy

of sampling schedule increases as the number of sample decreases. Energy of sampling schedule containing 20 or more samples converged to nearly zero.

Table 3 Minimum energy, final energy and performance error of RSS

Number of sample	Minimum Energy	Final Energy	Performance error (%)
5	50.045	50.197	0.30
6	31.490	31.490	0.00
7	20.825	21.000	0.84
8	11.624	11.715	0.78
9	8.553	8.554	0.01
10	6.907	6.908	0.01
15	2.320	2.320	0.00
20	0.682	0.687	0.73
25	0.348	0.350	0.86
30	0.348	0.348	0.00
mean	**13.843**	**13.913**	**0.37**

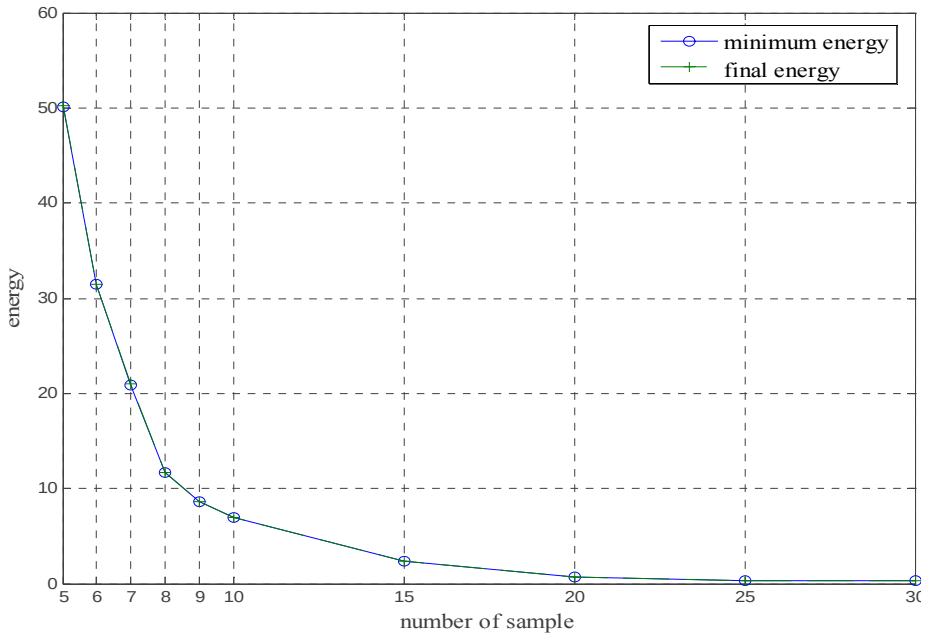


Figure 23 Minimum and final energy of RSS obtained from the SA algorithm at each number of samples in schedule

2. Optimal Number of Sample and OSS of Simulated Data

S_I^{RSS} errors against numbers of samples are shown in Figure 24. The values of S_I^{RSS} and percentage error are shown in Table 4. The error increases abruptly when the number of sample is less than 7. At 15 samples or more the error converges close to zero. The red dash line in Figure 24 represents the error bound of the OSS specified in this study. The optimal number of sample for NGT is 7 samples. Table 5 shows the mean RSS of each number of sample. The mean RSS diagrams are shown in Appendix A.

Table 4 S_I^{RSS} and percentage error of NGT data

Number of sample	S_I^{RSS} **(10^{-4} min^{-1}(μU/ml)$^{-1}$)**	**Percentage error**
5	12.841	6.95
6	12.774	6.39
7	12.335	2.73
8	12.291	2.37
9	12.240	1.94
10	12.217	1.75
15	12.133	1.05
20	12.093	0.72
25	12.433	0.78
30	12.402	0.40

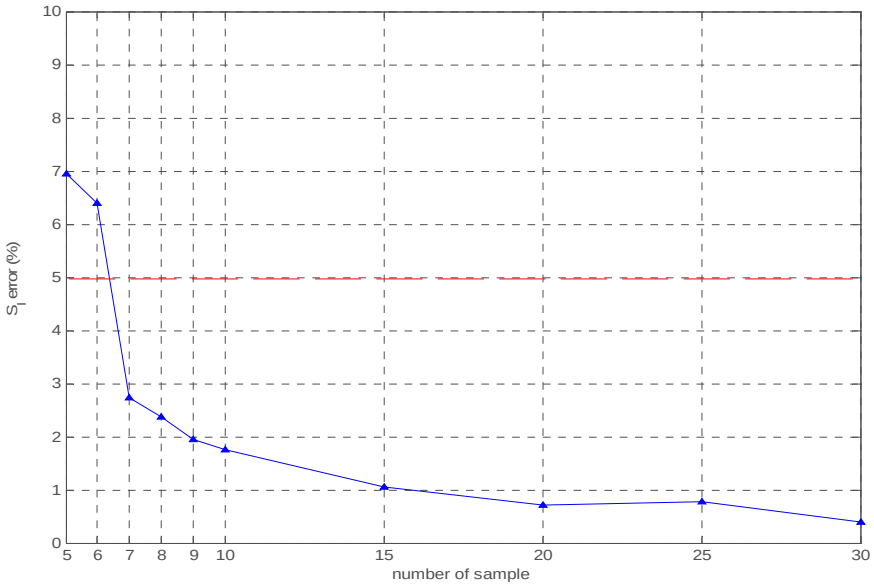


Figure 24 Percentage error of S_I from RSS at different numbers of sample. The red dash line represents the percentage error bound of OSS

Table 5 Mean RSS with different numbers of sample

		RSS (min)																			
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Number of sample	**5**	0	61	132	174	300															
	6	0	62	126	151	190	300														
	7	0	60	100	133	158	194	300													
	8	0	56	69	116	136	160	197	300												
	9	0	57	70	113	129	147	172	203	300											
	10	0	56	68	95	119	134	151	173	206	300										
	15	0	52	59	66	73	93	111	121	131	143	156	171	191	218	300					
	20	0	51	57	63	68	74	85	104	111	118	126	133	141	150	161	173	186	203	225	300
		RSS (min)																			
Number of sample	**25**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
		0	36	53	58	63	67	72	82	87	103	109	115	121	127	133	140	147	155	163	173
		21	**22**	**23**	**24**	**25**															
		183	196	211	230	300															
	30	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
		0	22	49	55	60	65	70	79	83	88	103	108	113	117	122	127	131	136	142	148
		21	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**										
		154	161	169	177	185	195	207	223	258	300										

3. Monte Carlo Simulation

Figure 25 describes the distribution of time points for each sample in OSS from 30 simulated data sets. The boxplot depicting five-number summary consists of median (red vertical line), lower quartile and upper quartile (left and right edges of blue box), and the minimum and maximum values (left and right whiskers). The red plus sign represents the outlier. Range of time for t_2 to t_6 is between 52 and 210 min. The overlap of each sampling time can be observed. The distribution of t_2, t_4, t_5 and t_6 is close to normal distribution, while t_3 has a positive skew and higher dispersion than other sampling time. Table 6 summarizes the statistical values of each sampling time in optimal sampling schedule.

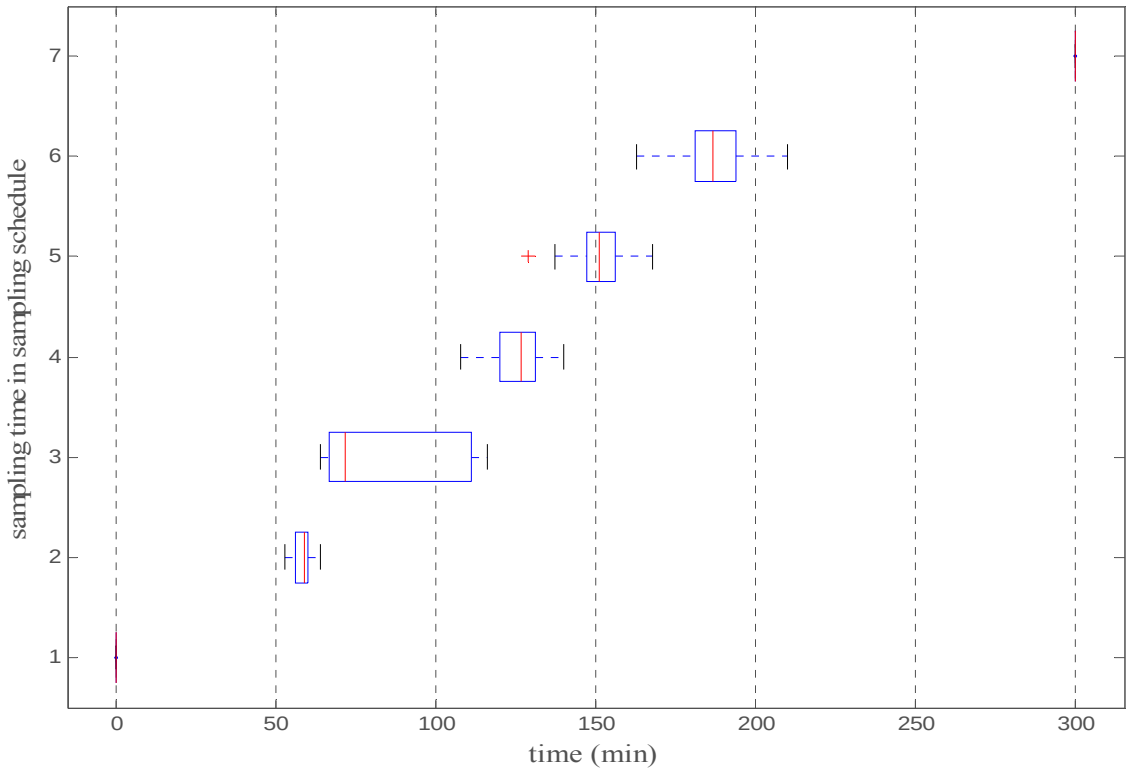


Figure 25 Boxplot of distribution of time point in sampling schedule from Monte Carlo Simulation

Table 6 Statistical values of each sample in OSS from Monte Carlo simulation

	t_1	t_2	t_3	t_4	t_5	t_6	t_7
Median	0	59	72	126.5	151	186.5	300
Mean	0	58.33	85.03	125.73	150.83	187.07	300
SD	0	2.796	21.511	7.683	8.742	10.901	0
Min	0	53	64	108	129	163	300
Max	0	64	116	140	168	210	300

The robustness of OSS against noise was evaluated. S_I^{FSS} and S_I^{OSS} estimated from data corrupted with noise agrees well with correlation coefficients more than 0.840 for every level of noise. S_I error increases as noise variance increases. Figure 26 shows the percentage error of S_I^{OSS} with respect to different variability of noise. Glucose concentration data corrupted by noise with variance more than 12 resulted in errors exceeding the OSS criteria in this study.

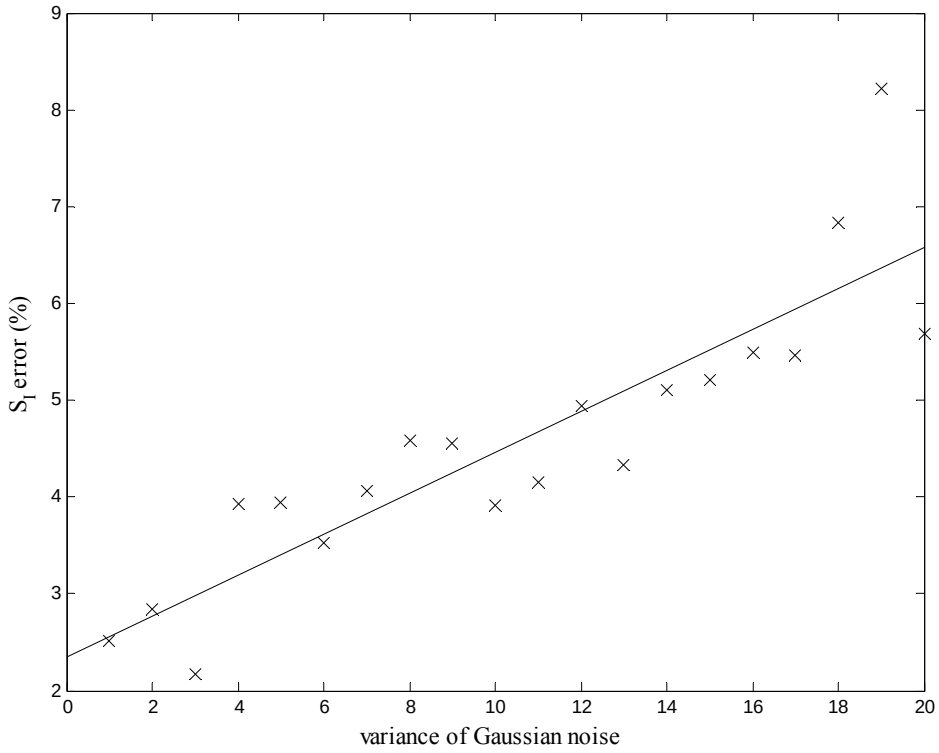


Figure 26 The robustness of OSS against noise

4. Validation of the RSS with Human Experiment Data

Due to the limited number of sample taken in each experiment, each subject cannot be validated with the same RSS. The individual RSS of subject 1, 2 and 3 together with S_I^{RSS} are shown in Table 7, 8 and 9, respectively. The result shows that error in S_I estimation decreases as the number of sample in RSS decreases. Individual RSS of subject 1 give better S_I estimation than other subjects. In case of subject 3, S_I value obtained RSS with 14 samples was very close to the S_I estimated from experimental sampling schedule which consisted of 22 samples. The OSS of each subject based on the criteria in this study was 6 samples for subject 1, 9 samples for subject 2, and 10 samples for subject 3. The sampling schedule diagram of these OSS is shown in Figure 27, Figure 28 and Figure 29. The RSS diagram of each subject is shown in Appendix A.

Table 7 Individual RSS of subject 1

Number of sample	RSS (min)							S_I^{RSS*}	Percentage error
5	0	60	120	180	300			13.099	7.937
6	0	60	120	150	180	300		12.619	3.988
7	0	60	90	120	150	180	300	12.504	3.034

*Unit of S_I measurement: 10^{-4} $min^{-1}(\mu U/ml)^{-1}$. S_I^{FSS} =12.135x10^{-4} $min^{-1}(\mu U/ml)^{-1}$

Table 8 Individual RSS of subject 2

Number of sample	RSS (min)									S_I^{RSS}	Percentage error
5	0	60	120	180	300					11.148	16.658
6	0	60	120	150	180	300				8.3131	13.004
7	0	60	90	120	150	180	300			8.9612	6.222
8	0	50	60	90	120	150	180	300		9.0345	5.455
9	0	50	60	90	120	150	180	210	300	9.6492	0.978

S_I^{FSS} =9.556x10^{-4} $min^{-1}(\mu U/ml)^{-1}$

Table 9 Individual RSS of subject 3

Number of sample	RSS (min)														S_I^{RSS}	error
5	0	60	135	180	300										25.725	41.438
6	0	60	120	150	195	300									14.935	17.885
7	0	60	90	135	150	195	300								20.012	10.027
8	0	60	75	120	135	165	195	300							19.748	8.573
9	0	60	75	120	135	150	180	210	300						19.354	6.409
10	0	60	75	90	105	135	150	180	210	300					18.712	2.878
14	0	45	60	75	90	105	120	135	150	165	180	195	225	300	18.212	0.129

$S_I^{FSS} = 18.188 \times 10^{-4}\ \text{min}^{-1}(\mu\text{U/ml})^{-1}$

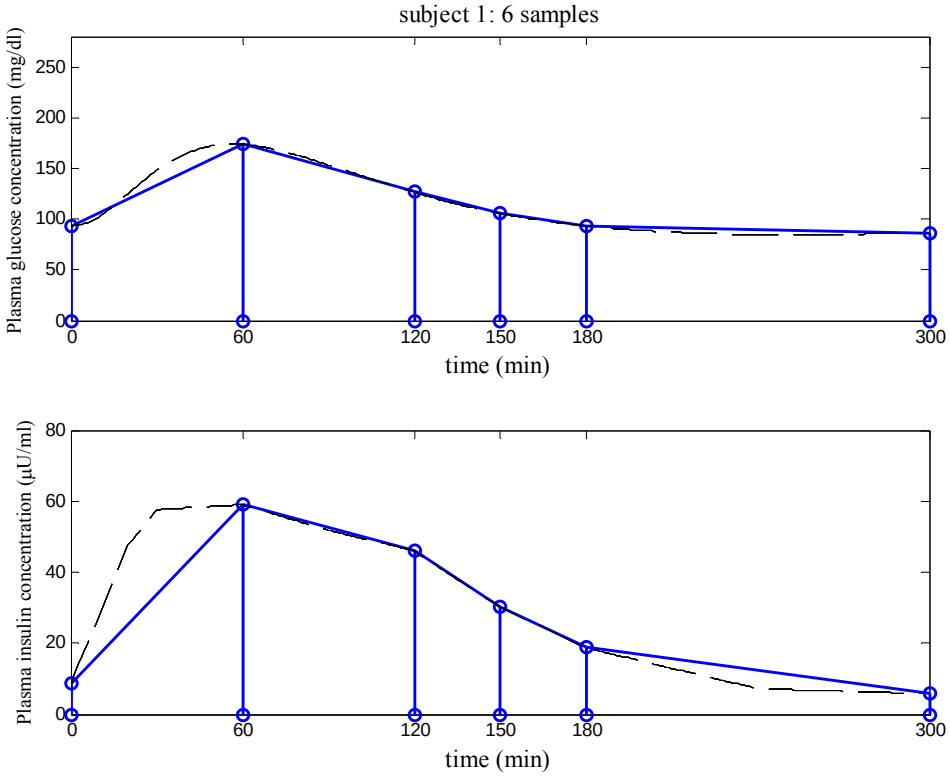


Figure 27 Individual OSS with 6 samples of subject 1

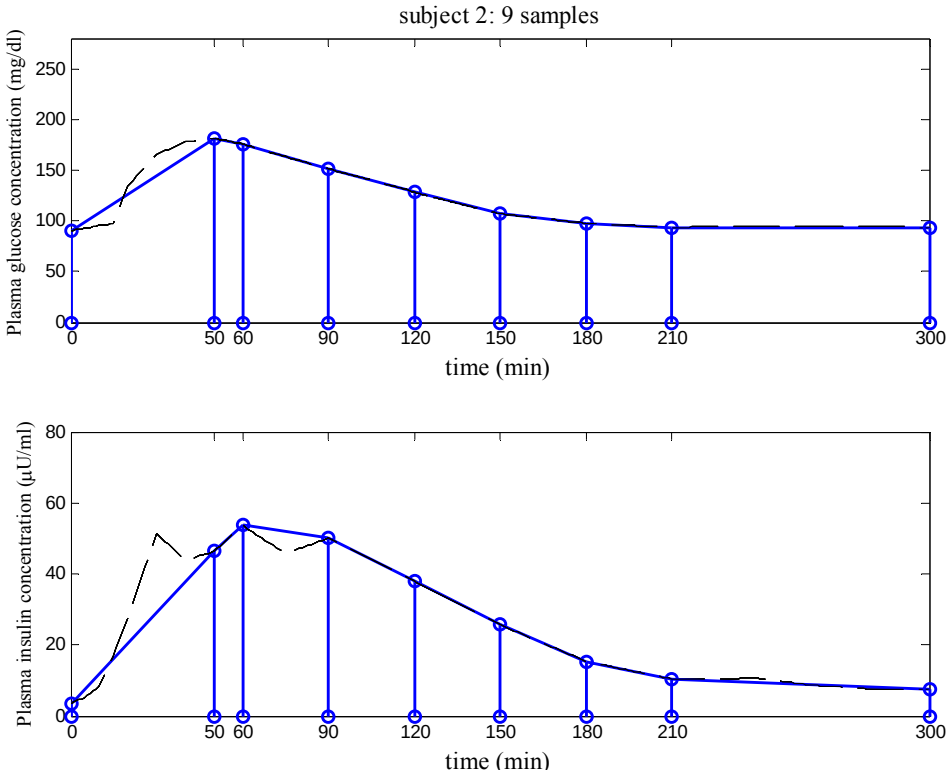


Figure 28 Individual OSS with 9 samples of subject 2

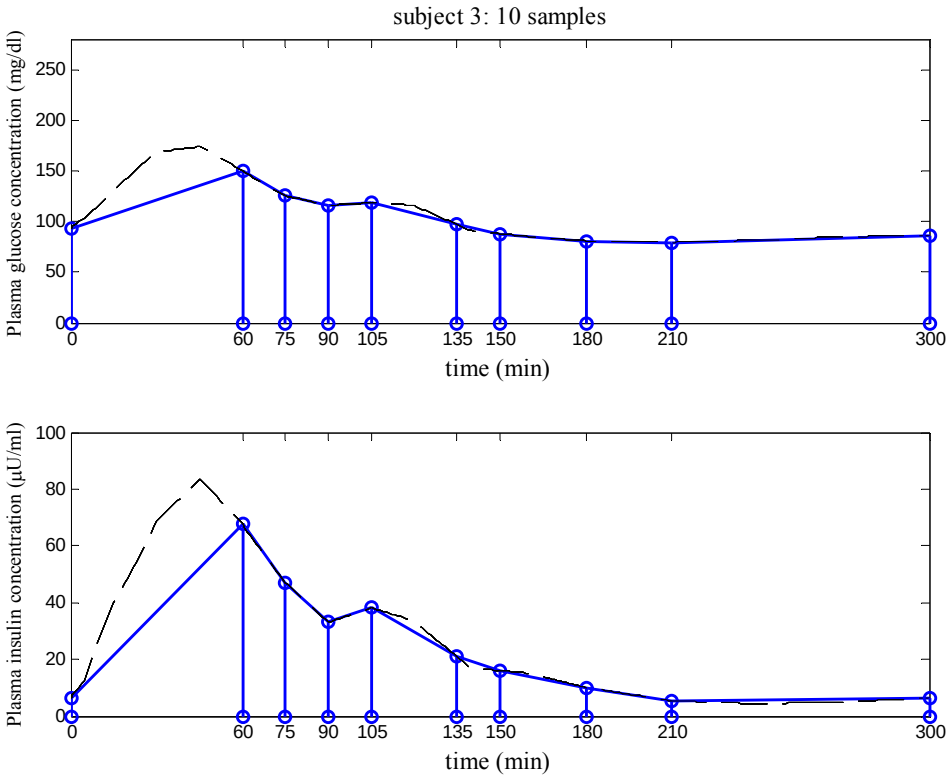


Figure 29 Individual OSS with 10 samples of subject 3

CHAPTER V
DISCUSSION

This chapter discusses the experimental results from the previous chapter. Performance of simulated annealing algorithm and the importance of objective function are discussed in the first section followed by the optimal number of sample and the optimal schedule of simulated data. The Monte Carlo simulation and OSS population are discussed in section 3 followed by the robustness of OSS against noise and validation of OSS with human data.

1. Performance of the Simulated Annealing Algorithm on Optimal Sampling Schedule Problem

The efficiency of the SA algorithm depends on control parameters such as initial temperature, cooling schedule, stopping criterion and the objective function. The initial control parameters in section 3.1.2 are general initial suggestion for all problems. The parameter that affected the SA algorithm performance in this study is the stopping criterion. The initial length of accepted chain, initially set at 4 temperatures, is too short. The energy of the final solution is much higher than the minimum energy the SA algorithm had found. The final solution is trapped in local minima. Changing the length of accepted criterion to 6 consecutive temperatures results in better performance.

It can be observed from Table 3 that the final energy is not equal to the minimum energy. This implied that the final solution from the SA algorithm is not always the best possible solution. This is because the nature of the SA algorithm is based on the randomness. The final solutions obtained from the SA algorithm were different at each time the algorithm was run. However, the SA algorithm with good control parameters promises that the final solution is not trapped in the local minima closest

to the starting point as occurred in other optimization algorithm. The final solution of the SA algorithm can then be acceptable. In case of the OSS problem in this study, the control parameter of SA algorithm showed in Table 2 results in the acceptable solution as specified in section 3.1.2. The difference between minimum energy and final energy is less than 1 percent for every case.

Energy of sampling schedule is inversely proportional to the number of samples. Since the energy is the mean squared error of glucose concentration estimated from linear interpolation, it implies that the more sample in schedule the more precision in estimating glucose concentration.

2. Reduced Sampling Schedule from Simulated Annealing

In order to relate the optimal sampling schedule design procedure to the estimation of S_I from oral glucose minimal model, MSE was weighted by information of model parameter sensitivity obtained from sensitivity analysis process. Sensitivity analysis analyzed how the variation of model parameter, p_1, p_2 and p_3, affected time course of glucose concentration. It gave information about which parameter was the best presenter of model and in which time interval.

The sampling schedule tested in this study can be divided into 2 groups based on number of samples in schedule; the frequent sampling (15 samples or more) and the reduced sampling(less than 10 samples). In case of frequent sampling number, the convergence of S_I estimation error was observed for all objective functions. These results implied that 20 samples was an adequate number in order to retrieve S_I with good precision. It could be seen that RSS obtained from obj_p3 resulted in better estimation of S_I while the RSS obtained from obj_p1 produced higher error than RSS obtained from other objective functions. The example of sampling schedule diagram obtained from obj_p1 in Figure 30a) shows that sampling schedule from obj_p1 is focused on time point around the maximum and the decreasing concentration region away from the maximum of glucose concentration. When considered the insulin action compartment, it can be seen that while the glucose concentration is around maxima the insulin action rate is low. In another word, the effect of insulin to reduce

blood glucose during this interval is not much. The glucose reduction around this time is the mechanism of glucose itself with little effects of insulin. This explanation fits well with the definition of p_1 which refers to the rate of insulin-independent glucose disappearance.

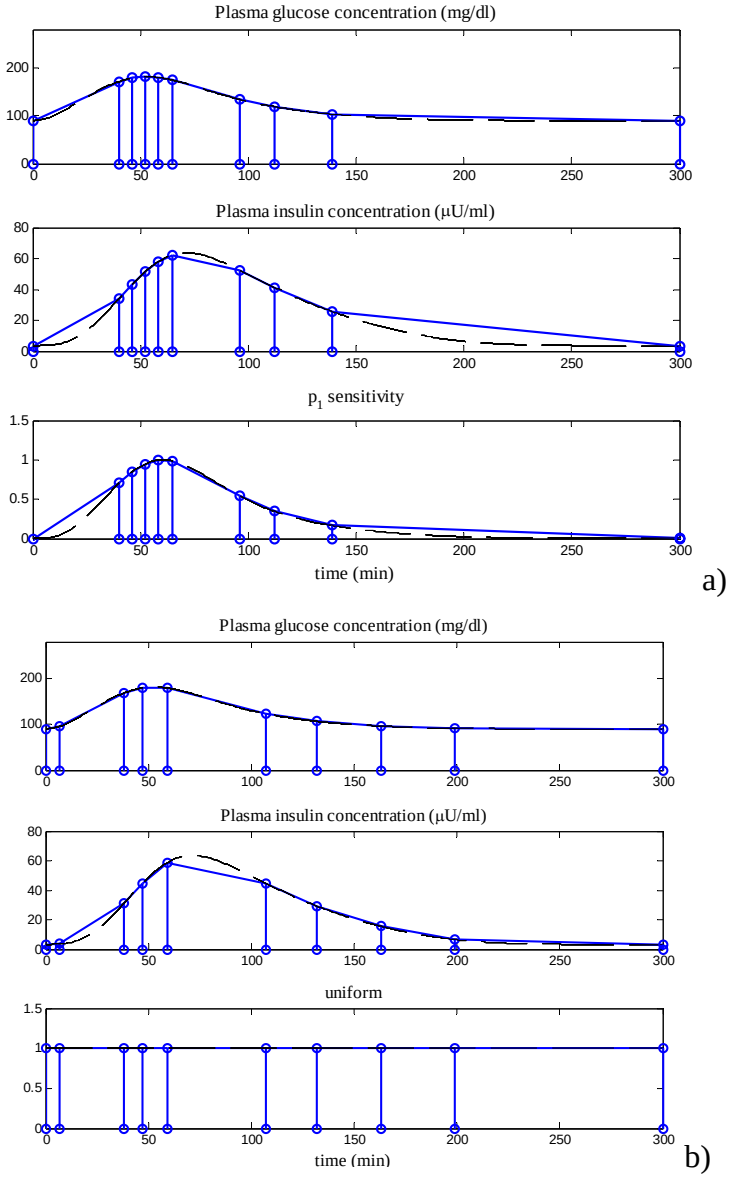


Figure 30 Ten-sample sampling schedule diagram obtained from a) obj_p1 b) obj_u

In case of reduced sampling number, error S_I estimated from RSS obtained from obj_u increases abruptly as the sample number decreases. This was because obj_u aimed at selecting schedule which best represent the glucose concentration based on

linear interpolation, the effects of model parameters were not taken into account. The sampling time selected by obj_u distributed in the beginning of the experiment, the peak concentration of glucose and the interval where glucose gradually decreased back to baseline. The obj_u showed better results than obj_p1 in frequent sampling since the sampling time distributed throughout the experiment interval but for the reduced sampling this distribution was not good for S_I estimation.

Obj_p_3 showed better results than other objective function in both frequent and reduced sampling number. S_I of minimal model was estimated from insulin action compartment $x(t)$ which is the auxiliary function represented the time delay effects of plasma insulin on blood glucose reduction. Parameter p_3 plays importance role in estimating S_I because it combines the rate of plasma insulin that transforms into insulin action together with the effect of insulin on blood glucose reduction so it determines S_I in great part. Sensitivity of p_3 is then an appropriate weighting function for linear interpolation estimation. The obj_p3 was then chosen to be used in the proposed simulated annealing algorithm. More details on sampling schedule selected by obj_p3 are described in the next section.

It can be concluded from this experiment that applying the information about the significance of each minute on S_I estimation to the objective function can improve the quality of RSS selected by simulated annealing algorithm. The proposed simulated annealing for OSS of OGTT data in this study is searched for the sampling schedule which minimizes the MSE of glucose concentration estimated by linear interpolation and weighted by information of parameter p_3 of oral glucose minimal model.

3. Optimal Number of Sample and Optimal Sampling Schedule of Simulated Data

The RSS with different numbers of sample in schedule had some common features. Time points of 0 and 300 min were fixed for all RSS by the assumption that the experiment started from baseline and completely returned to baseline again at the end of the experiment. The sampling interval in RSS can be divided into 2 intervals: the first interval around the peak concentration and the second interval around where

the concentration is gradually decreased to baseline. The latter is the interval where p_3 sensitivity is the highest. Figure 31 shows the example of RSS consisting of 10 samples. The time point between these two intervals was ignored due to the effect of linear interpolation together with the weighted values which caused the weighted mean squared error of this gap to be low. Estimating glucose concentration with higher order function may improve this issue and it will be tested in future developments.

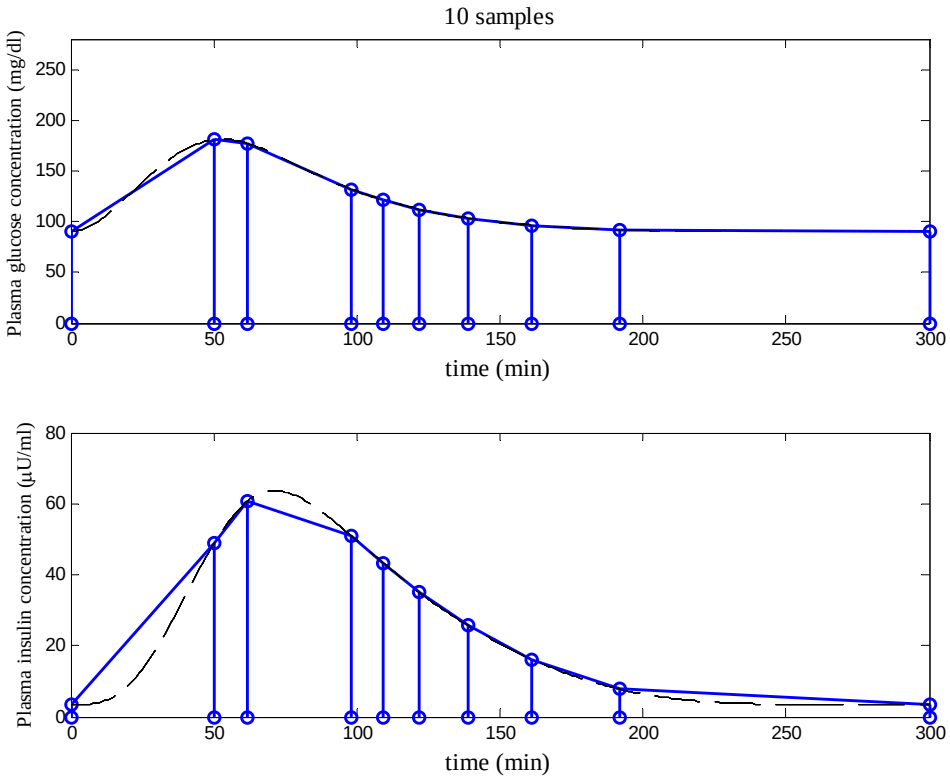


Figure 31 RSS diagram of 10 samples

The SA algorithm in this study is specific to each individual because the information about model parameter of individual is required prior to determining the RSS. The mean RSS with different numbers of sample obtained from three simulated data sets was then evaluated to obtain the RSS for general uses as shown in Table 5.

The average S_I error showed that the optimal sampling number for simulated OGTT data based on the criteria defined in this study was at 7 samples. This optimal

number was analyzed by using Monte Carlo simulation where random input were tested to observe the output.

Monte Carlo simulation in this study employed the uniform random parameters p_1, p_2 , p_3 and G_b to generate 30 simulated data sets and evaluate optimal sampling schedule of each set. Time points of each sample in OSS were analyzed to see how variation of data affected the distribution of time points. OSS consisted of 7 samples with the first and the last sample fixed at 0 and 300 min. The 2^{nd} to the 6^{th} sample were analyzed. Boxplot in Figure 25 shows that the time point in these samples has normal distribution except in the 3^{rd} sample. The 3^{rd} sample has wide range and more widely distributed nearer to the 2^{nd} sample. Though the time point of 3^{rd} sample cannot clearly define like others samples, it is still required to obtain better S_I estimation. The 2^{nd} sample had a narrow range distribution. It was distributed only around the peak concentration of glucose because the peak concentration is very important for estimating shape of concentration curve. The 4^{th} to 6^{th} samples were sampled around the returning to baseline which is important for p_3 estimation as previously mentioned.

Robustness of sampling schedule against different levels of noise was tested. The increasing noise variance deteriorated the quality of S_I estimated from FSS. The S_I estimated from OSS still correlated well with FSS. This can be implied that the OSS is still able to recover the S_I estimation from noisy data with acceptable quality compared to FSS estimation.

4. Validation with Human Experiment Data

The available data from experiment in human was performed with different sampling schedules. The individual RSS for each subject was obtained by modifying the RSS obtained from simulated data to the nearest experimental sample. The individual RSS for each subject was shown in Table 7, 8 and 9. The results showed that the optimal number of sample and optimal sampling schedule for each subject were different. In case of subject 1, the data consisted of 11 experimental samples. The individual RSS of subject 1 produced good S_I estimation compared with S_I

estimated from full experimental sampling schedule. RSS with 6 samples gave 3 percent S_I error, still within the error bound. This is because the characteristic of glucose concentration of subject 1 data is close to the simulated glucose profile. The time where glucose concentration reached maximum values and the time where glucose decreased to baseline of subject 1 data was close to that of simulated data. The individual RSS of subject 1 was able to collect the features of glucose concentration from these important intervals.

Experiment data of subject 2 consisted of 19 samples. The shape of glucose concentration curve of subject 2 was close to that of the simulated data. The individual RSS modified from simulated data seemed to cover both peak concentration interval and the region where glucose returned to baseline. However, the fluctuation of insulin concentration might be the factor that affects the estimation of S_I since the insulin concentration is used as an input to predict glucose concentration from minimal model.

In case of subject 3, it is obvious that the individual RSS completely missed the peak glucose concentration. The S_I estimation of this case was worse than other subject. The RSS of 10 samples from 22 experimental samples were needed in order to obtain the S_I estimation within error bound. The importance of sample taken at peak glucose concentration was confirmed in this experiment.

CHAPTER VI
CONCLUSION AND FURTHER DEVELOPMENT

Conclusion

This study proposes the method to find the optimal sampling schedule for estimating insulin sensitivity index from oral glucose test for an individual. The index was calculated from the oral minimal model. The main point of optimal schedule problem is to find the optimal number of sample in sampling schedule and the best configuration of that schedule. This study employs the simulated annealing algorithm because it is suitable for the combinatorial problem where the optimal configuration of parameters are needed. Moreover, it is easy to include the constraints such as how to move from one sampling schedule to another in simulated annealing algorithm. The proposed objective function to be minimized by simulated annealing is the mean squared error of glucose concentration estimated by weighted linear interpolation. Each sample point of OGTT data was weighted by the information from sensitivity of the oral minimal model with respect to parameters. Simulated annealing algorithm searches for the optimal configuration of sampling schedule with different reduced numbers of samples and calculate the insulin sensitivity index. The optimal sampling schedule was selected from the specific criteria based on the number of sample and the error of sensitivity index estimation. The optimal number of sample for simulated glucose and insulin profile according to the criteria in this study was 7 samples. It was also found that the number of sample adequate for precise estimation of the index was 20 samples. The reduced sampling schedule obtained from simulated data was tested on data from human experiment. The results of optimal sample number were different from those of simulated data and also different among subjects. It is recommended that reduced sampling schedule should include the peak glucose concentration in order to obtain good estimation of S_I .

Future Development

The interval where glucose concentration reaches its maximum should be studied in population because it is the promising feature of S_I estimation. The objective function taking the physiology of glucose-insulin interaction into account is another issue that should be further studied in future.

REFERENCES

1. Diabetes Atlas: executive summary. Brussels, Belgium: International Diabetes Federation; 2003.
2. Bergman RN, Ider YZ, Bowden CR, Cobelli C. Quantitative estimation of insulin sensitivity. American Journal of Physiology 1979;236(6):667-77.
3. Zijlstra E. Estimation of glucose kinetics and insulin sensitivity from an oral glucose tolerance test and use of two glucose tracers with a compartmental modelling approach. Practical training report: Department of Biomedical Engineering, Eindhoven University of Technology; 2004 March – July. Report No.: 04/BMTS04.
4. Gin H, Rugalleau V. Post-prandial hyperglycemia. Post-prandial hyperglycemia and diabetes. Diabetes & Metabolism(Paris) 2000;26:265-72.
5. Woerle HJ, Meyer C, Dostou JM, Gosmanov NR, Islam N, Popa E. Pathways for glucose disposal after meal ingestion in humans. American Journal of Physiology - Endocrinology & Metabolism 2003;284(4):716-25.
6. Martini FH, Bartholomew EF. Essentials of anatomy & physiology. New Jersey: Prentice-Hall 1997.
7. Clark MG, Wallis M, Barret E, et al. Blood flow and muscle metabolism: a focus on insulin action. American Journal of Physiology - Endocrinology & Metabolism 2003;284:241-58.
8. Radziuk J, Pye S. Tracer-determined glucose fluxes in health and type 2 diabetes: basal conditions. Best Practice & Research Clinical Endocrinology & Metabolism 2003;17(3):323-42.
9. Ganong WF. Review of medical physiology. 22 ed. San Francisco: McGraw-Hill; 2005.
10. Radziuk J. Insulin Sensitivity and Its Measurement: Structural Commonalities among the Methods. The Journal of Clinical Endocrinology & Metabolism 2000;85(12):4426-33.

11. Matthews D, Hosker J, Naylor B, Treacher D, Turner R. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28(412-419).
12. Katz A, Nambi SS, NMather K, et al. Quantitative insulin sensitivity check index: A simple accurate method for assessing insulin sensitivity in humans. The Journal of Clinical Endocrinology & Metabolism 2000;85:2402-10.
13. Soonthornpun S, Setasuban W, Thamprasit A, Chayanunnukul W, Rattarasanarn C, Geater A. Novel Insulin Sensitivity Indexl derived from oral glucose tolerance test. The Journal of Clinical Endocrinology & Metabolism 2003;88(3):1019-23.
14. McClatchey KD, ed. Clinical laboratory medicine. Philadelphia: Lippincott Wiliams & Wilkins; 2002.
15. Defronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. American Journal of Physiology - Endocrinology & Metabolism 1979;6(3):E214-E23.
16. Caumo A, Bergman RN, Cobelli C. Insulin Sensitivity from Meal Tolerance Tests in Normal Subjects: A Minimal Model Index. The Journal of Clinical Endocrinology & Metabolism 2000;85(11):4396–402.
17. Cobelli C, Foster D, Toffolo G. Tracer kinetics in biomedical research: from data to model. New York: Kluwer Academic; 2002.
18. Steele R. Influences of glucose loading and of injected insulin on hepatic glucose output. Annals of the New York Academy of Sciences 1959;82:420-30.
19. Natalucci S, Di Nardo F, Staffolani P, De Marzi C, Morosini P. Glucose absorption and insulin sensitivity from oral glucose tolerance test. In: the 25th annual international conference of the IEEE EMBS; 2003 September 17-21; Cancun, Mexico; 2003. p. 2758-60.
20. Schirra J, Katschinski M, Weidmann C, Schafer T, Wank U, Arnold R. Gastric emptying and release of incretin hormones after glucose ingestion in humans. Journal of clinical investigation 1996;97(1):92-103.
21. Di Nardo F, Casagrande F, Carle F, Boemi M, Fumelli P. Evaluation of insulin sensitivity from a minimal model adapted to oral glucose tests. Modelling in medicine and biology VI 2005;8:67-76.

22. Cobelli C, Ruggeri A. A Reduced Sampling Schedule for Estimating the Parameters of the Glucose Minimal Model from a Labeled IVGTT. IEEE Transactions on Biomedical Engineering 1991;38(10):1023-9.
23. Steil G, Volund A, Kahn S, Bergman R. Reduced sample number for calculation of insulin sensitivity and glucose effectiveness from the minimal model. Suitability for use in population studies. Diabetes 1993;42(2):250-6.
24. Coates PA, Ollerton RL, Luzio SD, Ismail IS, Owens DR. Reduced Sampling Protocols in Estimation of Insulin Sensitivity and Glucose Effectiveness Using the Minimal Model in NIDDM. Diabetes 1993;42:1635-41.
25. Nguyen H, Coates P, Luzio S, Owens D. A Reduced Sampling Protocol for The Identification of Insulin Sensitivity. In: 18th Annual International Conference of the IEEE Engineering in Medicine and Biology Society; 1996; Amsterdam; 1996. p. 2028-9.
26. Dalla Man C, Campioni M, Polonsky KS, et al. Two-Hour Seven-Sample Oral Glucose Tolerance Test and Meal Protocol: Minimal Model Assessment of beta-Cell Responsivity and Insulin Sensitivity in Nondiabetic Individuals. Diabetes 2005;54:3265-73.
27. Metropolis N, Rosenbluth AW, Rosenbluth MN, Teller AH. Equation of State Calculations by Fast Computing Machines. The journal of chemical physics 1953;21(6):1087-92.
28. Kirkpatrick S, Gelatt CD, Vecchi MP. Optimization by Simulated Annealing. Science 1983;220(4598):671-80.
29. Breda E, Cavaghan MK, Toffolo G, Polonsky KS, Cobelli C. Oral Glucose Tolerance Test Minimal Model Indexes of Beta-cell Function and Insulin Sensitivity. Diabetes 2001;50(1):150-8.
30. Dalla Man C. Oral glucose minimal models; formulation, validation, and use [Ph.D Thesis]. Italy: University of Padua; 2004.
31. Dalla Man C, Caumo A, Cobelli C. The oral glucose minimal model: Estimation of insulin sensitivity from a meal test. IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING 2002;49(5):419-29.

32. Charoentong P. Novel insulin sensitivity index derived from oral glucose tolerance test. [The degree of master of Engineering (Biomedical Engineering)]. Nakorn Pathom: Mahidol University; 2005.
33. Neatpisarnvanit C, Boston JR. Estimation of plasma insulin from plasma glucose. IEEE Transactions on Biomedical Engineering 2002;49(11):1253-9.
34. Khoo MCK. Physiological Control Systems. New York: IEEE Press; 2000.
35. Choi L, Caffo B, Rohde C. Optimal Sampling Times in Bioequivalence Studies Using a Simulated Annealing Algorithm. Johns Hopkins University, Dept of Biostatistics Working Papers 2004;59.
36. Thomaseth K, Cobelli C. Sensitivity Analysis in Parameter Estimation of Physiological Systems. In: 18th Annual International Conference of the IEEE Engineering in Medicine and Biology Society; 1996; Amsterdam; 1996. p. 1672-3.
37. Garcia Molla VM. Description of the MATLAB function SENS_SYS and SENS_IND. 2002. (Accessed at http://www.mathworks.com/ matlabcentral/fileexchange/loadFile.do?objectId=1480&objectType=file.)
38. Rutenbar RA. Simulated Annealing Algorithms: An Overview. IEEE Circuits and Devices Magazine 1989:19-26.
39. Aarts E, Korts J. Simulated Annealing and Boltzmann Machines: A stochastic Approach to Combinatorial Optimization and Neural computing. Essex, Great Britain: John Wiley & Sons; 1989.
40. Kendall G. Simulated Annealing. 2005. (Accessed at http://www.cs.nott.ac.uk/ ~gxk/aim/notes/simulatedannealing.doc.)
41. Vicini P, Cobelli C. The iterative two-stage population approach to IVGTT minimal modeling: improved precision with reduced sampling. American Journal of Physiology: Endocrine and metabolism 2001;280:179-86.
42. Krudys KM, Kahn S, Vicini P. Population approaches to estimate minimal model indexes of insulin sensitivity and glucose effectiveness using full and reduced sampling schedules. American Journal of Physiology: Endocrine and metabolism 2006;291:716-23.
43. Venkataraman P. Applied Optimization with MATLAB Programming. New York: John Wiley & Sons; 2002.

APPENDIX

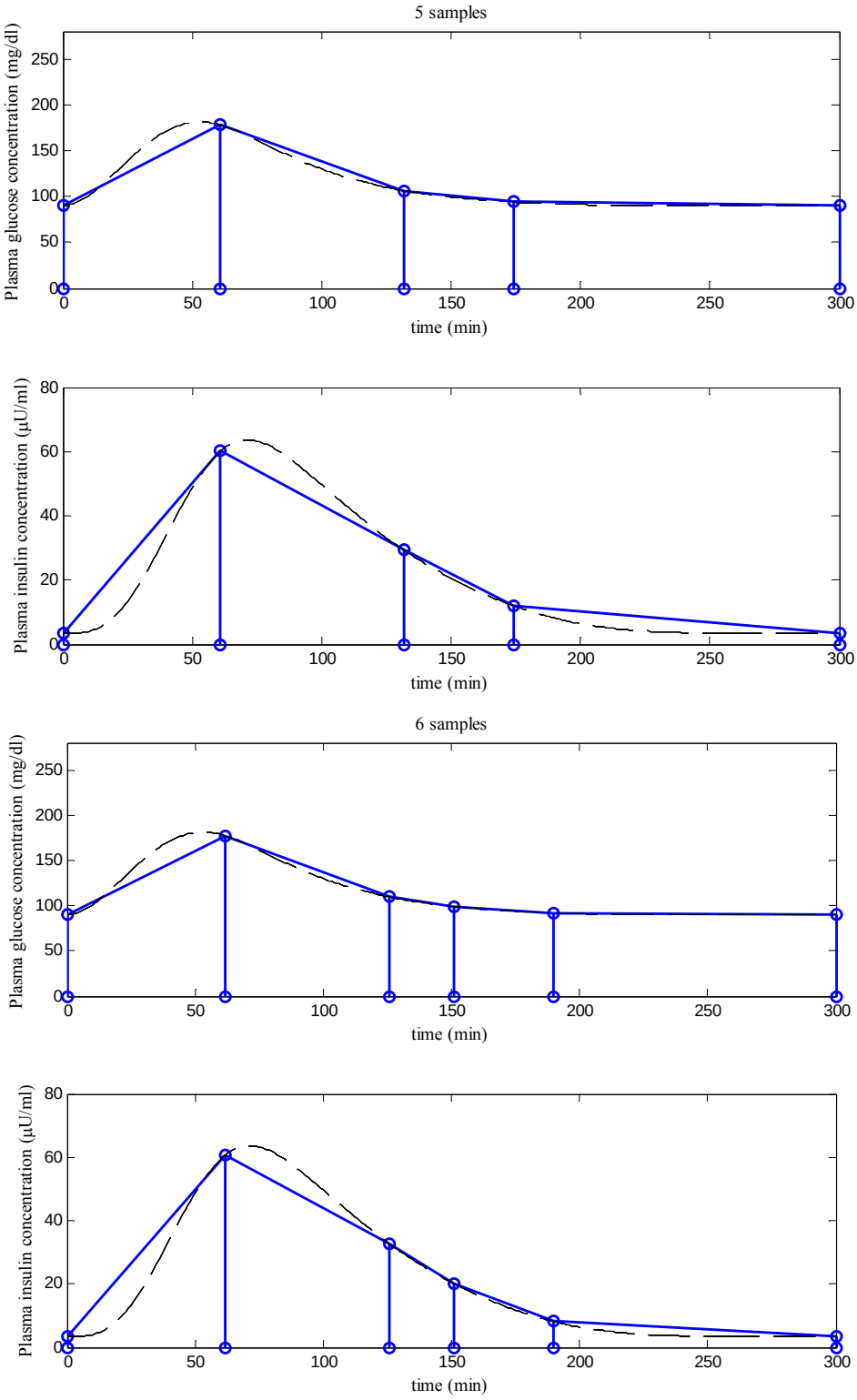


Figure A 1 Mean reduced sampling schedule diagram

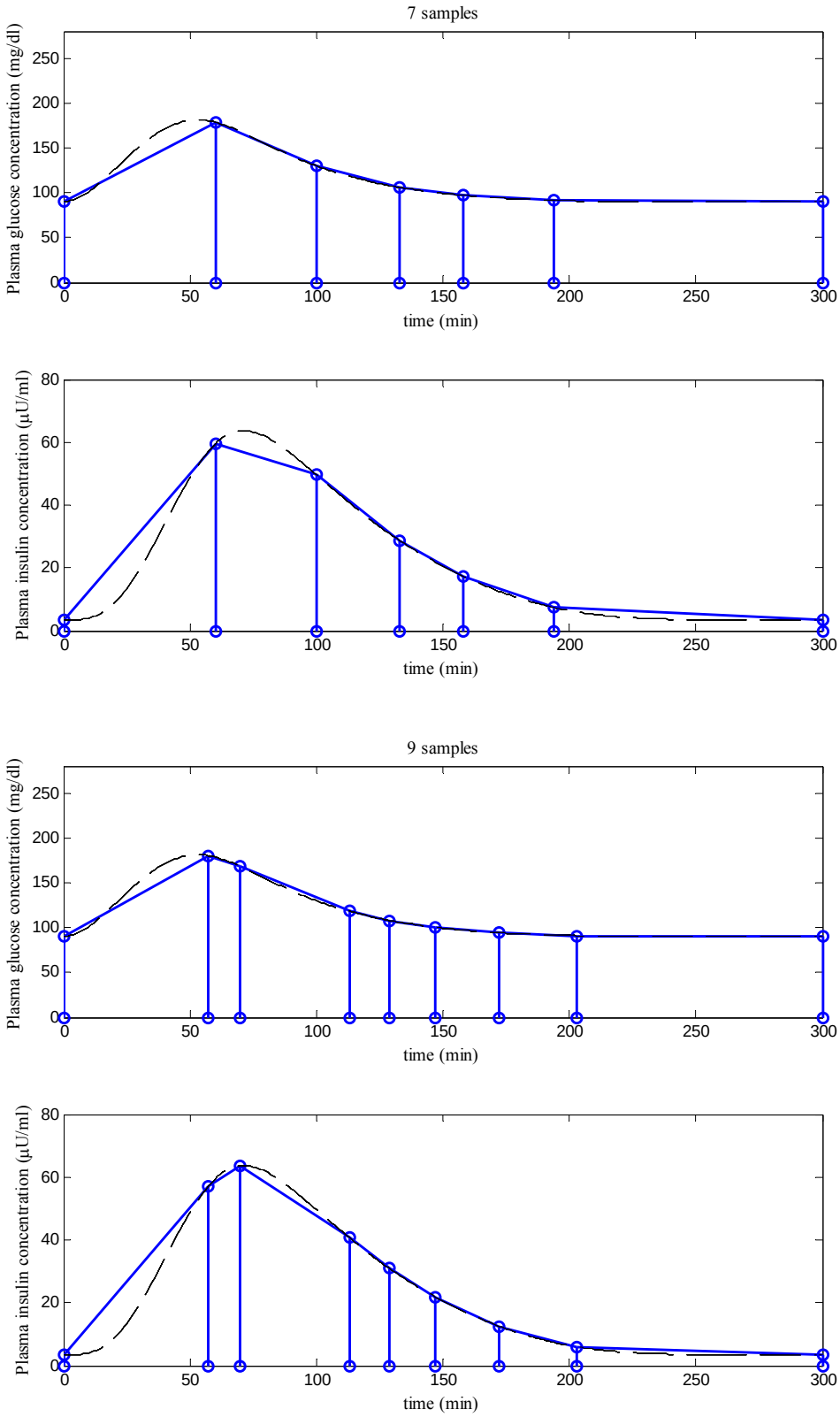


Figure A 1 Mean reduced sampling schedule diagram (continued)

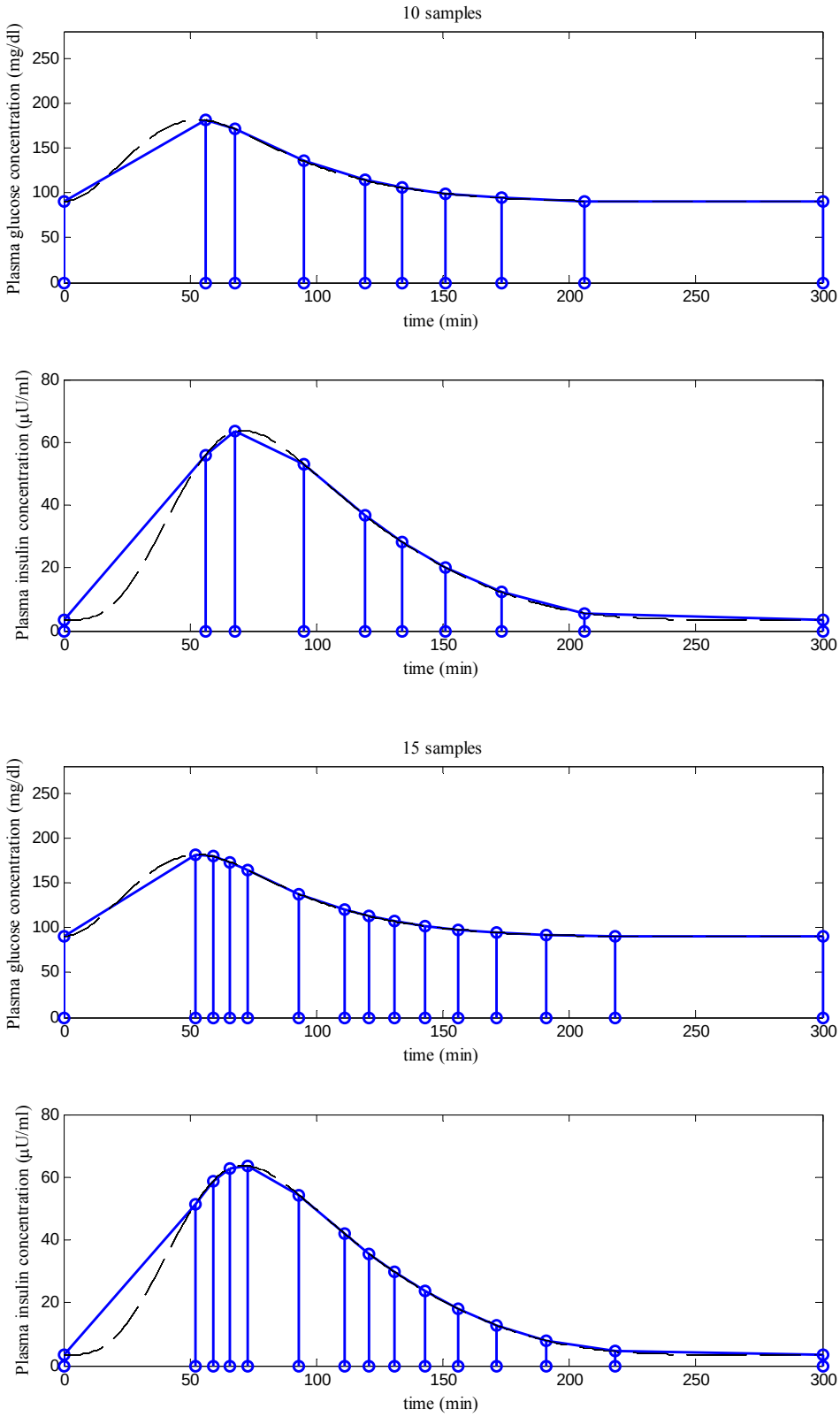


Figure A 1 Mean reduced sampling schedule diagram (continued)

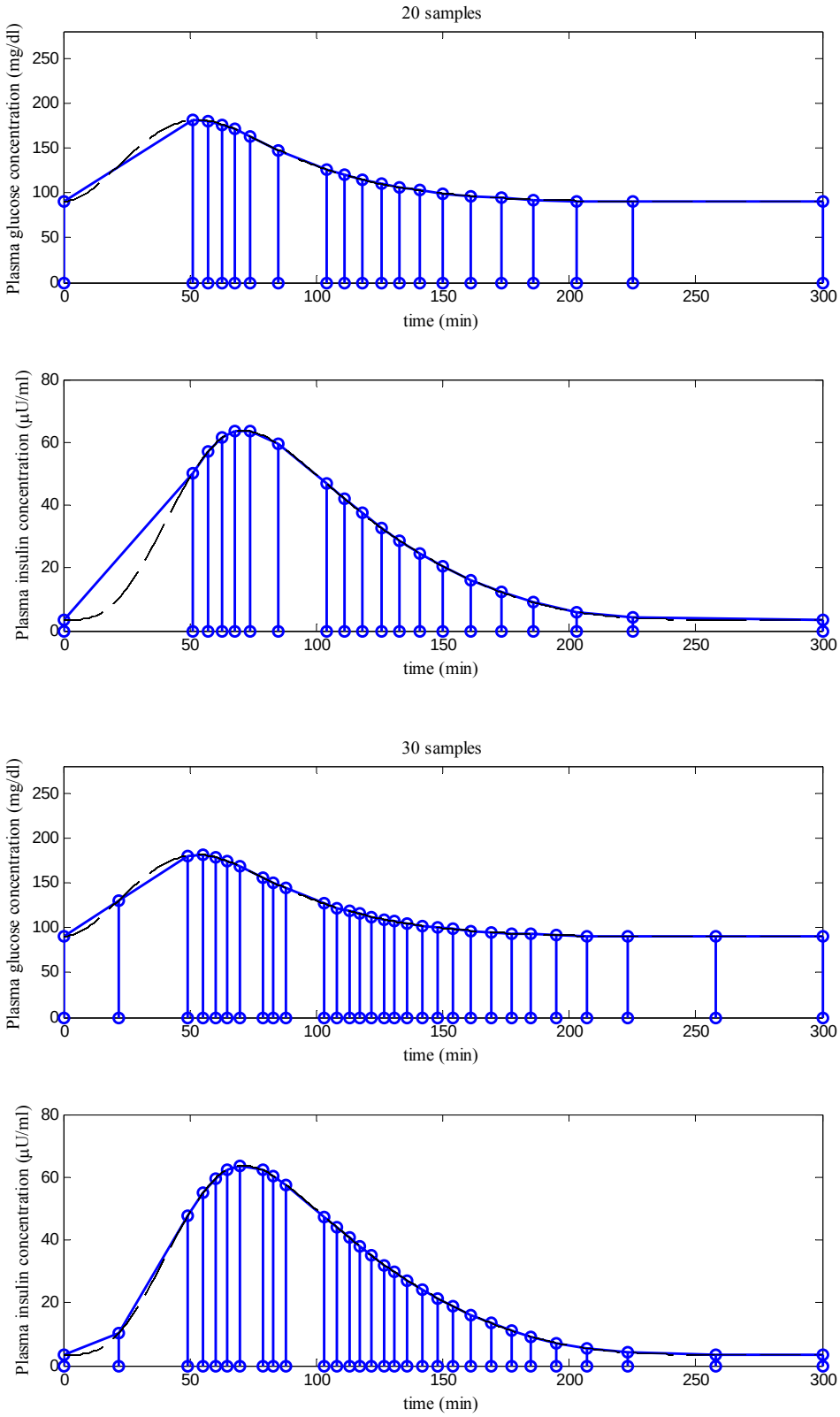


Figure A 1 Mean reduced sampling schedule diagram (continued)

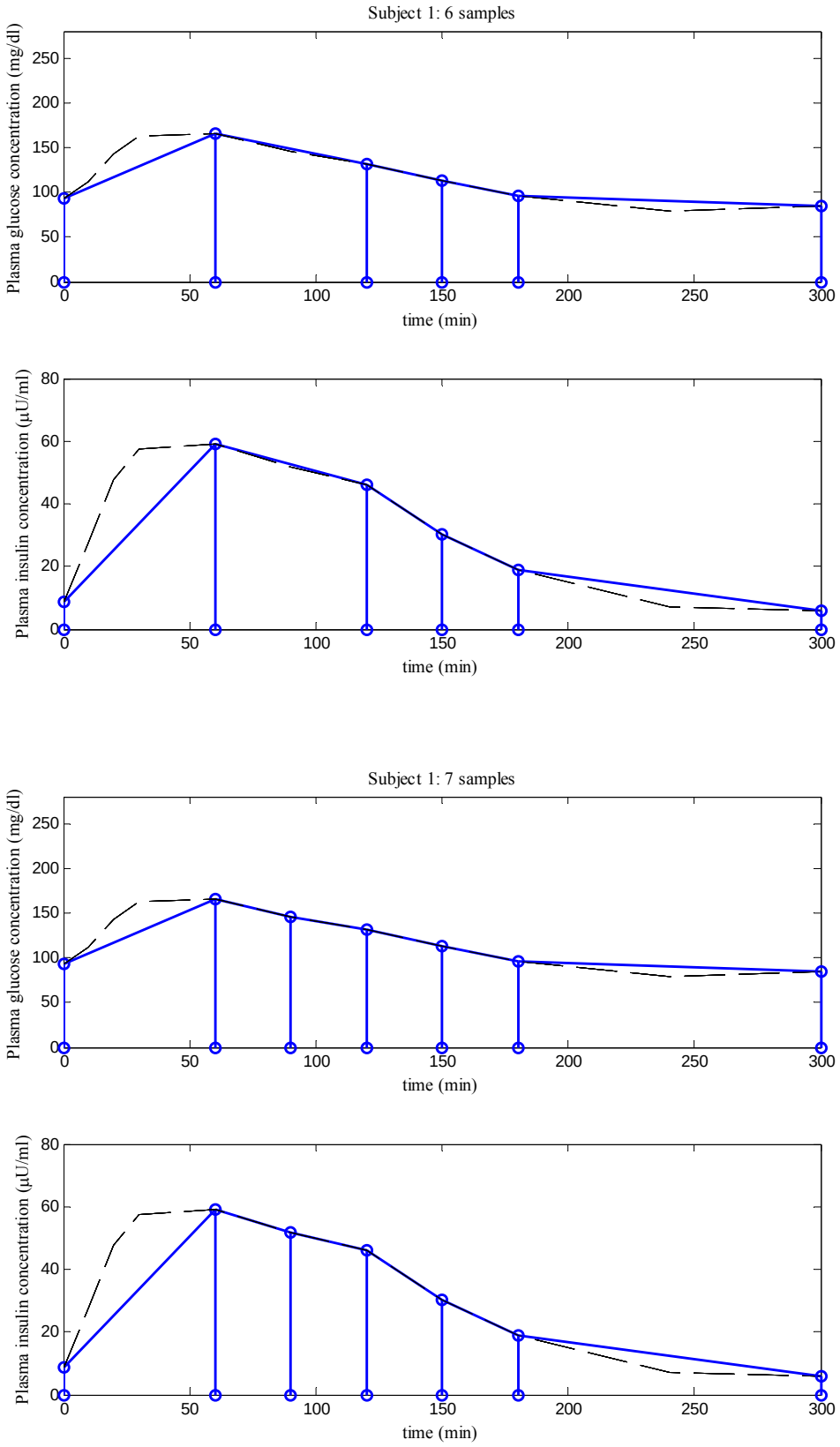


Figure A 2 Individual reduced sampling schedule diagram of subject 1

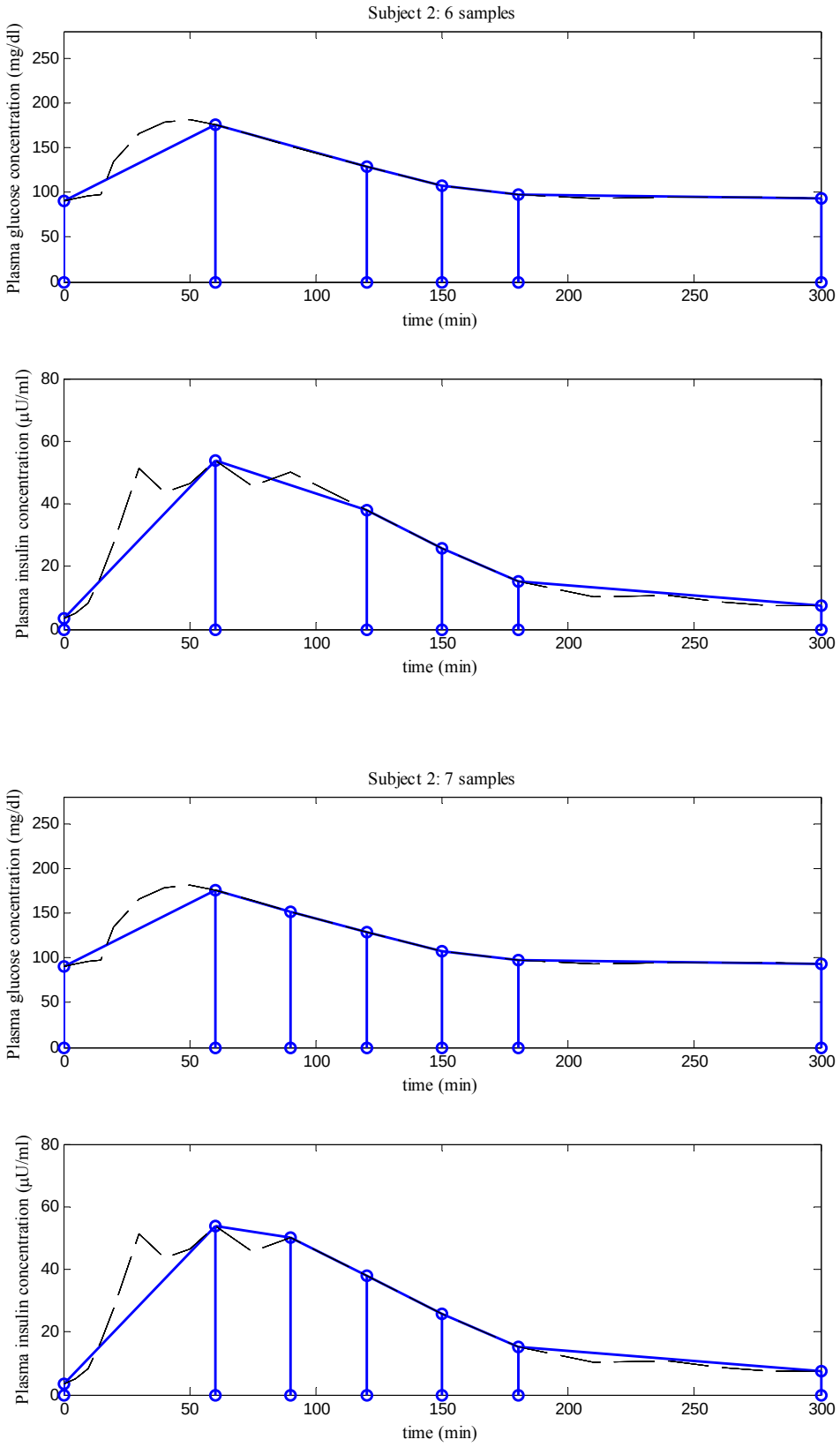


Figure A 3 Individual reduced sampling schedule diagram of subject 2

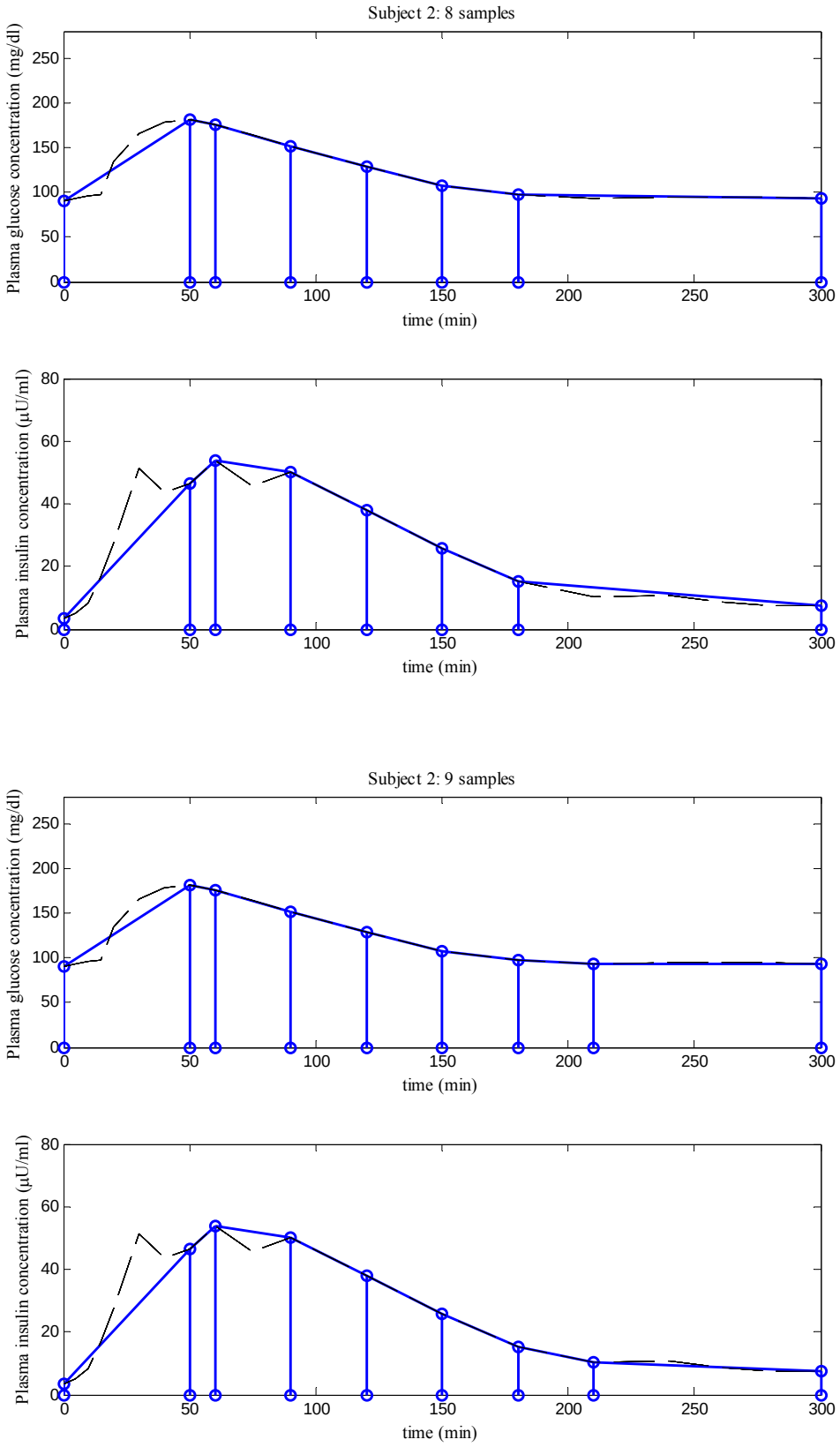


Figure A 3 Individual reduced sampling schedule diagram of subject 2 (continued)

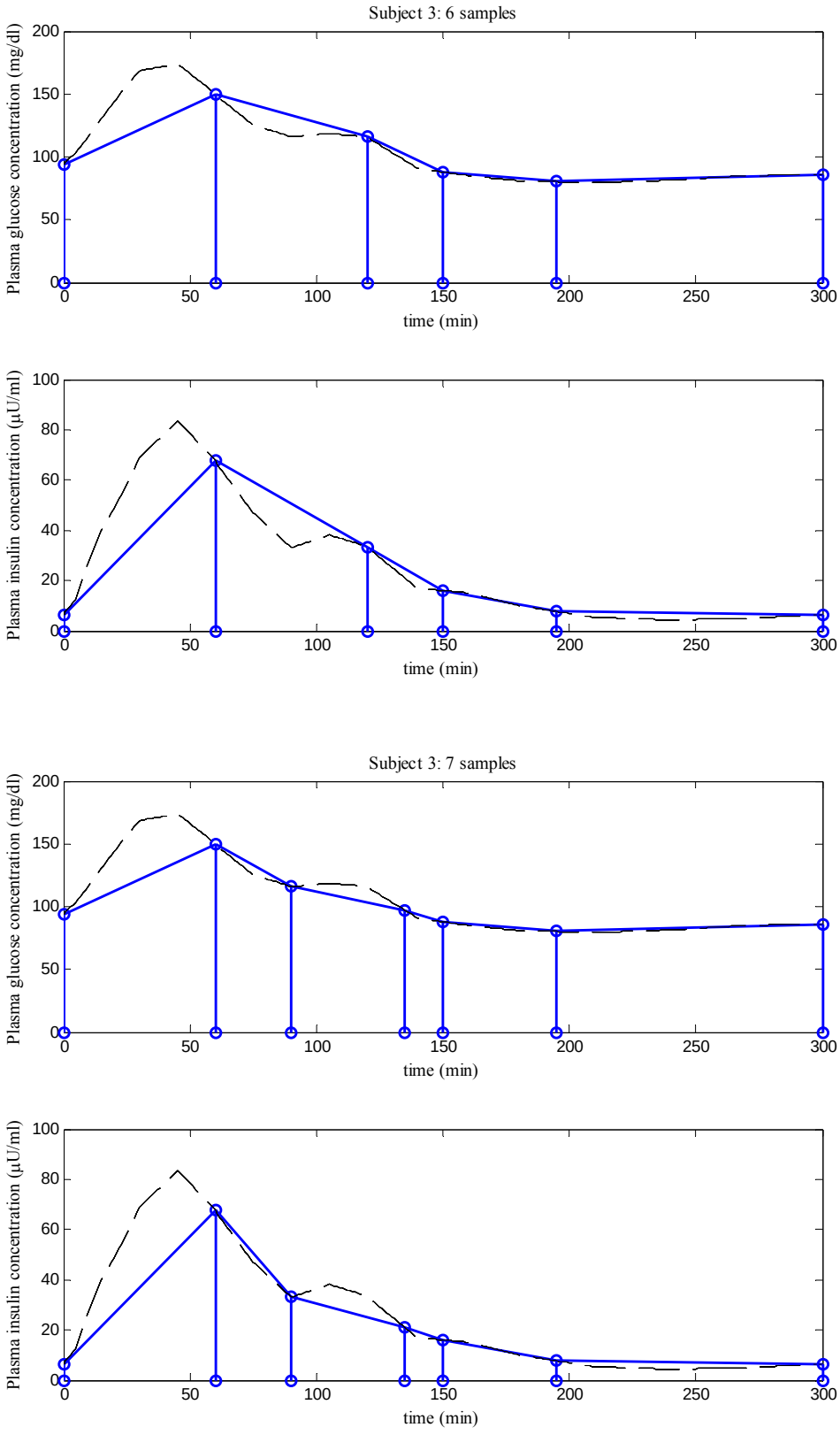


Figure A 4 Individual reduced sampling schedule diagram of subject 3

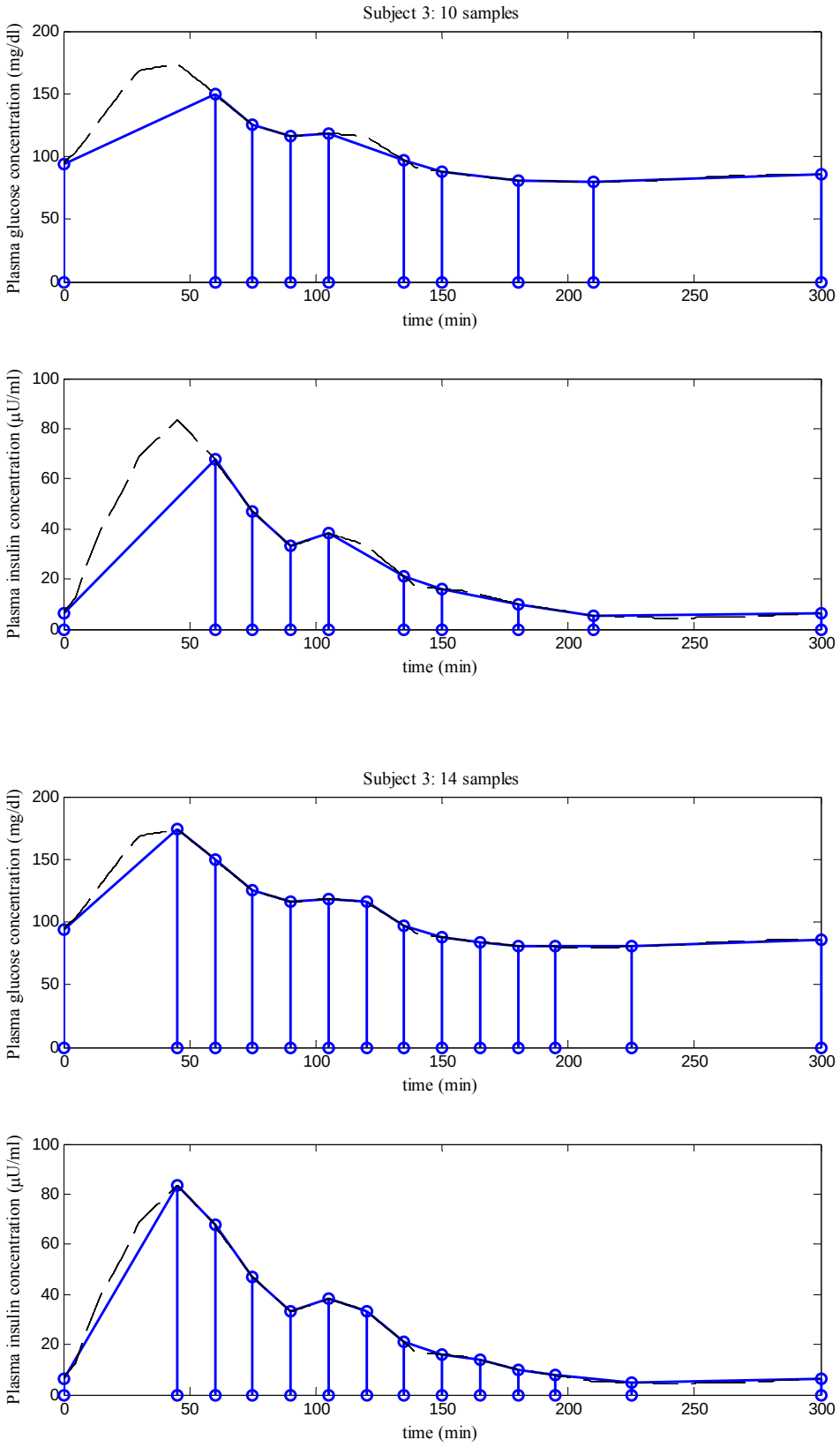


Figure A 4 Individual reduced sampling schedule diagram of subject 3 (continued)

Optimal Sampling Schedule for Oral Glucose Tolerance Test Data

Thanatip Chankong[1*] and Chatchai Neatpisarnvanit[2]

[1]Department of Biomedical Engineering, Faculty of Engineering, Mahidol University (Salaya Campus), Phutthamonthol, Nakorn Pathom 73170

[2]Department of Electrical Engineering, Faculty of Engineering, Mahidol University (Salaya Campus), Phutthamonthol, Nakorn Pathom 73170

E-mail: g4736131@student.mahidol.ac.th

ABSTRACT

Insulin sensitivity index is the index that measures the ability of insulin to regulate blood glucose level which is useful in treatment planning for diabetic patients. This index can be evaluated by several methods but there is a tradeoff between information and number of sample. Simple method require sample from a few time points but it cannot give much information about glucose-insulin response while complex method gives more information but also needs samples from more time points. Finding the optimal sampling schedule which requires a few samples but does not worsening the information will improve the efficiency of follow up procedure and treatment planning for diabetic patients.

The aim of this study is to reduce the number of blood samples required for estimating insulin sensitivity index from oral glucose minimal model, the mathematical model that describe the glucose-insulin interaction when the body system is challenged by oral glucose dose, using . SA is a global minimization search and is suitable for problem with many variables. The objective function to be minimized is the error between glucose concentration obtained from full sampling schedule (300 samples in 300 minutes) and the estimated glucose concentration obtained from reduced sampling schedule represented by linear interpolation function. S_I^{300} . The reduced sampling schedule which has the fewest number of samples and the error of S_I^{RSS} is not exceed 5 percent of S_I^{300} is said to be the optimal sampling schedule (OSS). The results show that the error of S_I^{RSS} obtained from reduced sampling schedules with sample less than 7 is beyond the expected error bound. The reduced sampling schedule with 7 samples is then chosen to be the optimal sampling schedule.

Keywords

Glucose Minimal Model, Insulin Sensitivity Index, Oral glucose Tolerance Test, SA

1. INTRODUCTION

Diabetes Mellitus is a metabolism disorder results from abnormality in insulin production or the use of insulin, a hormone released from pancreas to regulate glucose concentration in blood. Eighty percent of diabetes patients are noninsulin-dependent diabetes (NIDDM) or type II diabetes which is characterized by two defects; the insulin is produced insufficiently and peripheral tissues are less sensitive to the insulin (insulin resistance). A problem of diabetic patient is not only the abnormal of blood glucose, but also lead to many complications such as blindness, kidney failure, and poor circulation in lower limb. It also relates to cardiovascular disease which is the first cause of death in Type II diabetic patient. Several researches have been working on measuring insulin sensitivity, the

ability of insulin to control glucose production and utilization. This index is useful for treatment planning and evaluating the efficacy of therapy. Euglycemic hyperinsulinmic clamp method, the gold standard method of measuring insulin sensitivity index, is an effective way to estimate the dynamical interaction of glucose and insulin. It is, however, not suitable for population study or clinical use due to its high cost and complex procedure. The cheaper and simpler method for estimating the index which is widely used is the glucose tolerance test (GTT). This test challenges the glucose-insulin regulation system by external glucose dose and monitors the dynamic physiological response. The classical glucose tolerance test applied the bolus of glucose by intravenous injection direct into blood circulation and is called the intravenous glucose tolerance test (IVGTT). The problem of IVGTT is simplified by assuming that the bolus injection is a pulse with known dose. The minimal model developed by Bergman et al. [2] is the widely accepted method to assess the IVGTT information. However, the appearance of bolus of glucose in blood is not the real life situation. The blood glucose regulation mechanism does not depend solely on glucose appears in blood, but also depend on other factors such as stimulation via glucose absorption in the gut. To avoid the disadvantages of IVGTT, the oral glucose tolerance test (OGTT) has been used. The problem of modeling OGTT becomes more complex since the glucose appears in blood circulation come from ingested glucose that is slowly absorbed in the gut. To evaluate the insulin sensitivity from OGTT based on the classical Bergman's minimal model, the model of glucose absorption in the gut is coupled with the minimal model [16, 19, 21, 31]. The major disadvantage of using oral glucose minimal model is that blood samples at many time points are needed for model identification, at least 30 samples over 4-5 hours, which is not suitable for clinical use and epidemiological studies.

Several researches worked on reducing the number of sample needed to estimate insulin sensitivity index from minimal model but most of them focus on the IVGTT[23-26, 41, 42]. The aim of this study is to develop the optimal sampling schedule for OGTT which minimize the number of samples required while maintaining the error not to exceed the specific error bound. The SA algorithm is the optimization method used in this study.

2. MODEL FORMULATION

2.1 The Oral Glucose Minimal Model

The oral glucose minimal model consists of the classical minimal model (Equation 1-3) coupled with the glucose absorption model (equation 4) proposed by Di Nardo [21]. It is assumed that the rate of glucose absorption is equal to the rate of glucose appears in the plasma. The rate of glucose appearance, Ra, is the input of the oral glucose minimal model.

$$\frac{dG(t)}{dt} = -p_1\left[G(t)-G_b\right] - X(t)G(t) + \frac{R_a(t)}{VW}; \quad G(0)=G_b \tag{1}$$

$$\frac{dX(t)}{dt} = p_2 S_I\left[I(t)-I_b\right] - p_2 X(t); \qquad X(0)=0 \tag{2}$$

$$\frac{dI(t)}{dt} = \gamma\left[G(t)-h\right]t - nI(t); \qquad I(0)=0 \tag{3}$$

$$\frac{dG_g(t)}{dt} = R_s(t) - \left[R_a(t) - r_l(t)\right]; \qquad G_g(0)=0 \tag{4}$$

where G(t) is plasma glucose concentration at time t [mg/dl]; I(t) is plasma insulin concentration at time t [μU/ml]; X(t) is the remote insulin in action which affect the net glucose appearance [min^{-1}]; $R_a(t)$ is the rate of glucose appearance in the blood [mg/dl] which is assumed to be linearly related to the glucose mass in the gut $G_g(t)$ [21]; VW is glucose distribution volume [dl]; p_1 is the rate of insulin-independent glucose disappearance [min^{-1}]; p_2 is the rate for decrease of tissue glucose uptake ability [min^{-1}]; n is the first order decay rate for plasma

insulin [min^{-1}]; h is the threshold value for plasma glucose above which the pancreatic β-cell release insulin [mg/dl]; γ is the rate of endogenous insulin secretion with glucose concentration above h [$(\mu U/ml)min^{-2}(mg/dl)^{-1}$]; G_b is baseline plasma glucose [mg/dl]; I_b is baseline plasma insulin [μU/ml]; S_I is insulin sensitivity index [$min^{-1}(\mu U/ml)^{-1}$] which is the ability of insulin to control glucose production and utilization. The detail of rate of ingested glucose appearance into the circulation is described in section 2.2.

2.2 The Rate of Glucose Appearance in Blood Circulation Model

The glucose absorption model assume that the ingested glucose dose leaves the stomach and enter the gut compartment with rate $R_s(t)$. Some glucose is extracted and utilized by liver and intestine with rate $R_l(t)$. The rest of glucose, so called the post hepatic glucose, is absorbed and appear in blood circulation with rate $R_a(t)$. The glucose flux from stomach into gut compartment [20] is described by the following equation:

$$R_s(t) = D \cdot \ln 2 \cdot 2^{-\left[(t-t_i)/\tau\right]^{\beta}} \cdot \frac{\beta}{\tau}\left[\frac{t+t_i}{\tau}\right]^{\beta-1}; \qquad 0 \le t \le 300\,\text{min} \tag{5}$$

where D is the ingested glucose dose [mg]; t_i is the delay time of glucose administration [min]; τ is the time that half of glucose dose D has been delivered; and β is the parameter of gastric retention decay curve. The glucose is delivered from gut with the rate proportional to the amount of glucose mass by constant k_d. Glucose from gut is absorbed and enters the blood circulation with fraction value of 0.87. Therefore, the rate of ingested glucose appearance in blood is described by

$$R_a(t) = 0.87 \cdot k_d \cdot G_g(t) \tag{6}$$

3.SAMPLING SCHEDULE OPTIMIZATION

3.1 SA Algorithm

SA algorithm (SA) is analogy to the mechanical annealing used to harden glass and metal. The annealing process consists of two steps; increase the heat to a maximum value at which the solid melts and then carefully decrease the temperature until the particles are arranged in the ground state. At high temperature the atoms can move freely through states of higher energy. At each lowered temperature, if cooled slowly enough, the metal reaches the global minimum energy state, the atoms lose the mobility and line in the most stable orientation and form a pure crystal. If a melted metal is cooled too fast or quenched, the metal might not escape from a local minimum energy and will ends up in a polycrystalline or amorphous state.

In 1953, Metropolis proposed the algorithm to simulate the evolution of a solid in a heat bath to thermal equilibrium based on Monte Carlo technique. Begin with initial configuration i, the new configuration j is randomly selected then evaluate the change of energy, $\Delta E = E_j - E_i$. Instead of choosing configuration randomly then weight with $\exp\left(-\Delta E / kT\right)$ as in classical Monte Carlo method, the Metropolis Monte Carlo algorithm choose configuration with probability $\exp\left(-\Delta E / kT\right)$ and weight them evenly. If the new configuration has lower energy, $\Delta E < 0$, it is accepted as the starting point of the next selection. If the new configuration is worse, it may be acceptable with a probability that depends on the energy difference and current temperature (equation 7). Accepting worse configuration allow the search algorithm to jump out of the local minima.

$$P\{accept\} = \begin{cases} 1 & if \;\; \Delta E \le 0 \\ \exp\left[-\left(\dfrac{\Delta E}{T}\right)\right] & if \;\; \Delta E > 0 \end{cases} \tag{7}$$

where T is the control parameter analogy to temperature in mechanical annealing. This acceptance rule is known as Metropolis criterion. The cooling schedule, a sequence of decreasing temperature, is the factor to moderates the acceptance. At higher temperature, a number of worse configuration will be accepted, as temperature decreased, only a few of them will be accepted and the algorithm finally move downhill similar to the steepest descent method. Probability of accepting bad move is implemented by comparing acceptance probability with a random number generated from a uniform distribution on the interval [0,1).

3.2Optimal Sampling Schedule by SA

The SA algorithm is employed in this study for the reason that the problem of finding the optimal sampling schedule involves many parameters (sampling time). The algorithm employed in this study is adapted from [35] where the SA is used to evaluate the optimal sampling schedule in pharmacokinetics study. The description of the proposed algorithm is as follow:

1. Set the number of move at each temperature, L=1000, and the initial temperature, T.
2. Set the initial reduced sampling schedule of m samples, $t=t_{1,}$,.., t_m.
3. Randomly choose a time point t_k from $t_1,\ldots,t_m$ then select the new time point t_{knew} from the time point between t_{k-1} and t_{k+1}. Replace t_k with t_{knew} to generate the new sampling schedule.
4. Calculate the energy difference between current schedule and new schedule, $\Delta E = E_{new} - E_{current}$ .The energy is calculated from the objective function described in section 3.3
5. Check whether the new schedule should be accepted determine by acceptance criterion (equation 7).
   - if the new schedule has lower energy, it is always accepted. Replace the current schedule with new schedule.
   - If the new schedule has higher energy, then generate random number r from [0, 1) and compare with acceptance probability $P = \exp(-\Delta E / T)$. Accept the new schedule if $P \geq r$.
6. Repeat step 3 to 5 for L times.
7. Calculate the next temperature from cooling schedule, $T = \alpha T$, where α =0.90.
8. Repeat whole process until the final energy improvement across four consecutive temperatures is less than 10 percent.

3.3The Objective Functions

The objective function to be minimized is the mean squared of error between the concentration curve and the estimated value using linear interpolation. The linear interpolation $g_i(t)$ from t_i to t_{i+1} is denoted as

$$\widehat{g}_i(t) = a_i t + b_i \qquad for\, t_i \leq t \leq t_{i+1} \tag{11}$$

where $a_i = \dfrac{g_{i+1} - g_i}{t_{i+1} - t_i}$, $b_i = \dfrac{g_i t_{i+1} - g_{i+1} t_i}{t_{i+1} - t_i}$

The mean squared error of linear interpolation is

$$obj_{linear} = \sum_{i=1}^{m-1} \int_{t_i}^{t_{i+1}} E\left\{\left[\widehat{g}_i(t) - g(t)\right]^2\right\} dt \tag{12}$$

4. METHODOLOGY

4.1 Database

Due to the cost and the difficulty of the experiment in human, glucose and insulin data are generated from equation 1-3 using MATLAB©. Parameters values for oral glucose model were taken from [21, 31] . Parameter values for insulin secretion compartment were taken from [33]. The full sampling schedule, sample every minute from 0 to 300 minutes, is generated and used as a reference data set.

4.2 Insulin Sensitivity Index Estimation

Insulin sensitivity index (S_I) of the oral minimal model is obtained by estimating the values of parameters in equation 1 and 2 based on experimental data. Parameter estimation is evaluated by nonlinear least square method using Levenberg-Marquardt algorithm implemented on MATLAB©.

4.3 Optimal Sampling Schedule

Nine set of reduced sampling schedules consist of 30, 25, 20, 14, 10, 8, 7, 6 and 5 samples are initialized. Each reduced sampling schedules is optimized using SA algorithm to find the best configuration. The insulin sensitivity index obtained from reduced sampling schedule, S_I^{RSS}, are estimated and compared with the reference evaluated from full sampling schedule, S_I^{300}. The reduced sampling schedule which has the fewest number of samples and the error of S_I^{RSS} is not exceed 5 percent of S_I^{300} is said to be the optimal sampling schedule (OSS).

5. RESULTS

The performance of SA algorithm is shown in figure 1. Figure 1a) shows the number of accepted move at each temperature. At the beginning of the algorithm where the temperature is high, the number of accepted move is nearly 1000 and decreasing until almost none of them is accepted. Figure 1b) shows that as the algorithm proceed, the energy difference of accepted move decrease and converge to zero. Figure 2 shows the reduced sampling schedules estimated from MSE of linear interpolation. The dash line represents the initial sampling schedule; the solid line represents the reduced sampling schedule evaluated by SA. The full sampling schedule index S_I^{300} is $12.007\times10^4\ \mathrm{min}^{-1}/\left(\mu U\cdot ml^{-1}\right)$. The reduced sampling schedules indexes, S_I^{RSS}, are shown in table 1. Values in the bracket show the error between S_I^{RSS} and S_I^{300}. The error of S_I^{RSS} obtained from reduced sampling schedules with sample less than 7 is beyond the expected error bound. Therefore, the reduced sampling schedule with 7 samples is chosen to be the optimal sampling schedule.

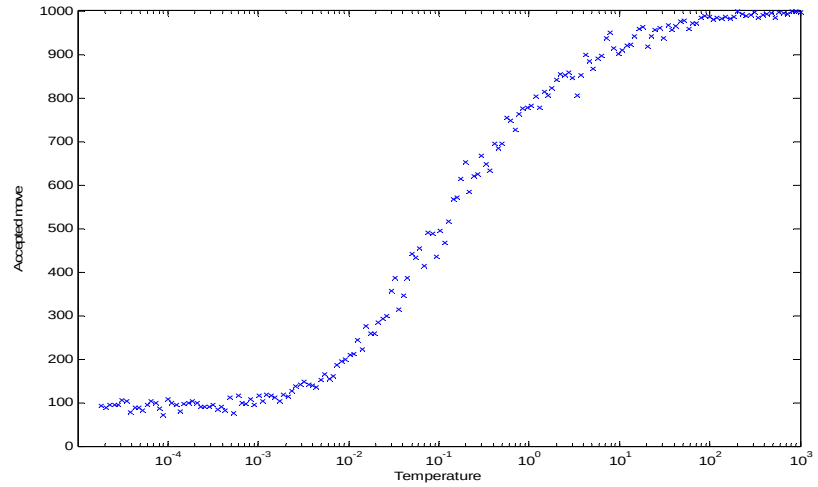
6. DISCUSSION

Searching for the optimal sampling schedule for the oral glucose tolerance test is a complex problem since it involves many parameters, i.e. time points in sampling schedule. SA has the advantage on other optimization method because the algorithm allows the search to jump out of the local minima and if the algorithm is run long enough, the solution space is reasonably explored to find the better solution. As the algorithm begins with high enough temperature, most of the moves, both good and bad, are accepted. As temperature slowly decreased and run long enough, less of bad move are accepted and finally almost none of them are accepted. The algorithm stops when the current sampling schedule seems to be the best one.

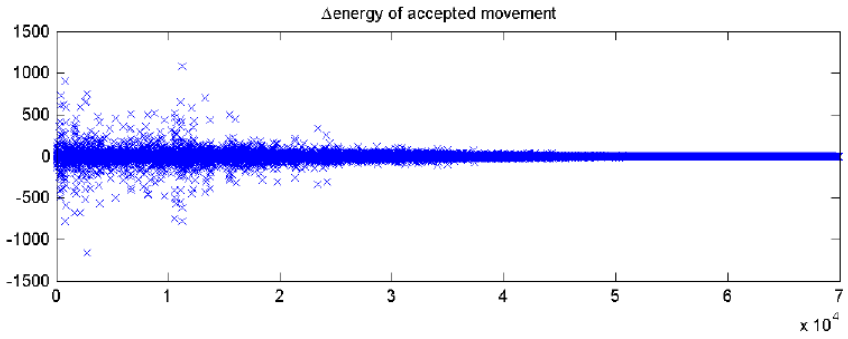
The next improvement of this study is to develop the objective function which taking the physiology of glucose-insulin interaction into account and apply the procedure to the real data.

Table 1. Insulin sensitivity index estimated from initial sampling schedule and reduced sampling schedule

Number of samples in sampling schedule	Insulin sensitivity index obtained from reduced sampling schedule, $S_I^{RSS}\left(\min^{-1}/\left(\mu U \cdot ml^{-1}\right)\right)$	Error (%) between S_I^{RSS} and S_I^{300}
300	12.007×10^{-4}	0.00
30	11.983×10^{-4}	0.20
25	11.975×10^{-4}	0.27
20	11.934×10^{-4}	0.61
14	11.923×10^{-4}	0.70
10	11.818×10^{-4}	1.57
8	11.773×10^{-4}	1.95
7	11.459×10^{-4}	4.57
6	11.300×10^{-4}	5.89
5	10.621×10^{-4}	11.54



a)



b)

Figure 1. a) The number of accepted movement at each temperature b) the energy difference of accepted move.

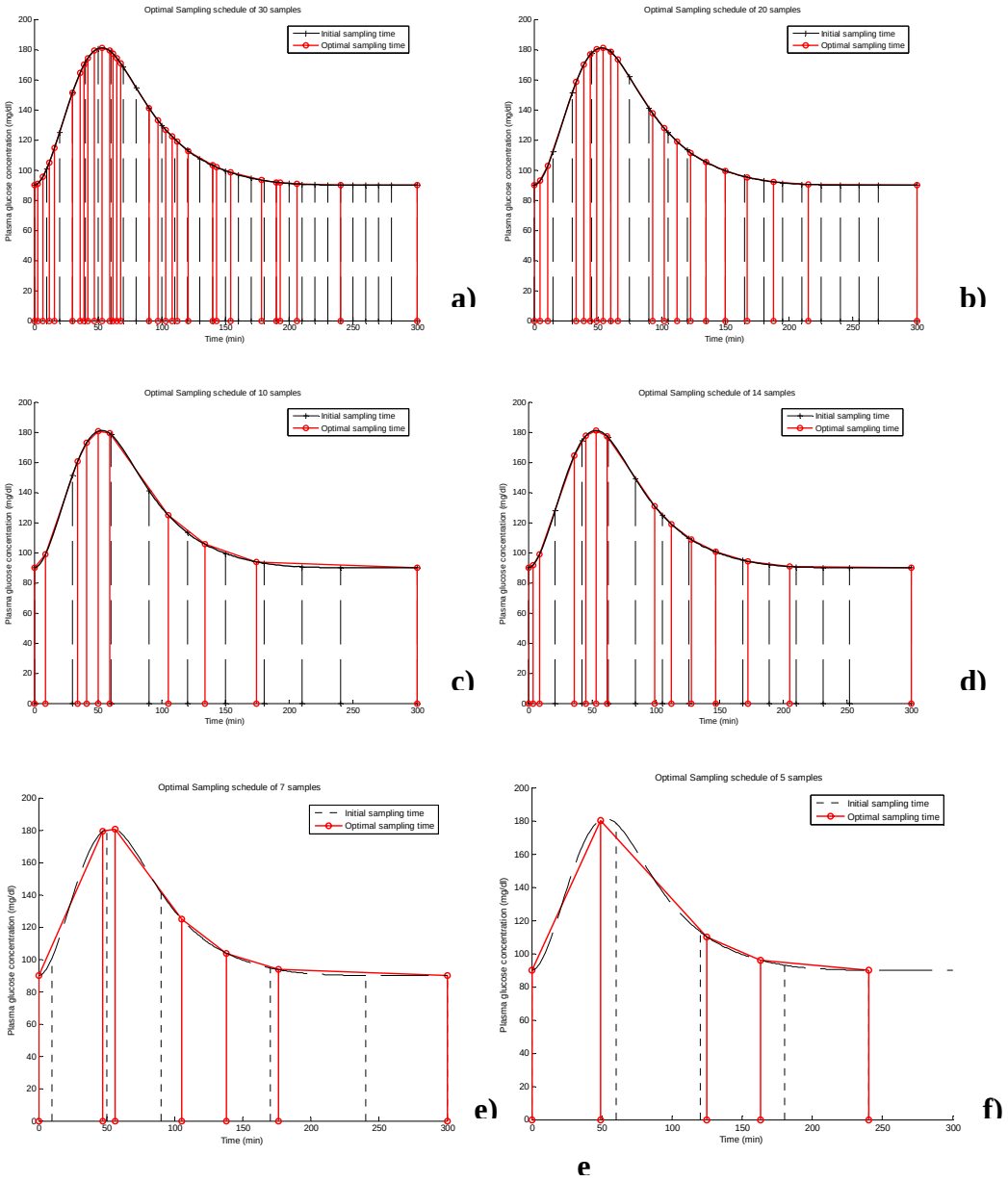


Figure 2. a) – f) The reduced sampling schedule consists of 30, 20, 14, 10, 7 and 5 samples, respectively.

7. REFERENCES

[1] Bergman, R. N., Ider, Y. Z., Bowden, C. R., Cobelli, C. Quantitative estimation of insulin sensitivity. American Journal of Physiology, 236, 6 (1979), 667-77.

[2] Natalucci, S., Di Nardo, F., Staffolani, P., De Marzi, C., Morosini, P. Glucose absorption and insulin sensitivity from oral glucose tolerance test. In: the 25th annual international conference of the IEEE EMBS (Cancun, Mexico, September 17-212003) Cancun, Mexico 2758-60.

[3] Caumo, A., Bergman, R. N., Cobelli, C. Insulin Sensitivity from Meal Tolerance Tests in Normal Subjects: A Minimal Model Index. The Journal of Clinical Endocrinology & Metabolism, 85, 11 (2000), 4396–402.

[4] Dalla Man, C., Caumo, A., Cobelli, C. The oral glucose minimal model: Estimation of insulin sensitivity from a meal test. IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING, 49, 5 (2002), 419-29.

[5] Di Nardo, F., Casagrande, F., Carle, F., Boemi, M., Fumelli, P. Evaluation of insulin sensitivity from a minimal model adapted to oral glucose tests. Modelling in medicine and biology VI, 8, (2005), 67-76.

[6] Nguyen, H., Coates, P., Luzio, S., Owens, D. A Reduced Sampling Protocol for The Identification of Insulin Sensitivity. In: 18th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (Amsterdam, 1996) Amsterdam 2028-9.

[7] Coates, P. A., Ollerton, R. L., Luzio, S. D., Ismail, I. S., Owens, D. R. Reduced Sampling Protocols in Estimation of Insulin Sensitivity and Glucose Effectiveness Using the Minimal Model in NIDDM. Diabetes, 42, (1993), 1635-41.

[8] Steil, G., Volund, A., Kahn, S., Bergman, R. Reduced sample number for calculation of insulin sensitivity and glucose effectiveness from the minimal model. Suitability for use in population studies. Diabetes, 42, 2 (1993), 250-6.

[9] Dalla Man, C., Campioni, M., Polonsky, K. S., et al. Two-Hour Seven-Sample Oral Glucose Tolerance Test and Meal Protocol: Minimal Model Assessment of beta-Cell Responsivity and Insulin Sensitivity in Nondiabetic Individuals. Diabetes, 54, (2005), 3265-73.

[10] Vicini, P., Cobelli, C. The iterative two-stage population approach to IVGTT minimal modeling: improved precision with reduced sampling. American Journal of Physiology: Endocrine and metabolism, 280, (2001), 179-86.

[11] Krudys, K. M., Kahn, S., Vicini, P. Population approaches to estimate minimal model indexes of insulin sensitivity and glucose effectiveness using full and reduced sampling schedules. American Journal of Physiology: Endocrine and metabolism, 291, (2006), 716-23.

[12] Schirra, J., Katschinski, M., Weidmann, C., Schafer, T., Wank, U., Arnold, R. Gastric emptying and release of incretin hormones after glucose ingestion in humans. Journal of clinical investigation, 97, 1 (1996), 92-103.

[13] Choi, L., Caffo, B., Rohde, C. Optimal Sampling Times in Bioequivalence Studies Using a SA Algorithm. Johns Hopkins University, Dept of Biostatistics Working Papers, 59, (2004).

[14] Neatpisarnvanit, C., Boston, J. R. Estimation of plasma insulin from plasma glucose. IEEE Transactions on Biomedical Engineering, 49, 11 (2002), 1253-9.

[15] Aarts, E., Korts, J. Simulaed Annealing and Boltzmann Machines: A stochastic Approach to Combinatorial Optimization and Neural computing. John Wiley & Sons, Essex, Great Britain, 1989.

[16] Ganong, W. F. Review of medical physiology. 22 ed. McGraw-Hill, San Francisco, 2005.

[17] Venkataraman, P. Applied Optimization with MATLAB Programming. John Wiley & Sons, New York, 2002

BIOGRAPHY

NAME	Miss Thanatip Chankong
DATE OF BIRTH	14 September 1980
PLACE OF BIRTH	Chiang Mai, Thailand
INSTITUTIONS ATTENDED	Chiang Mai University (1999-2001) Bachelor of Engineering (Electrical Engineering) Mahidol University (2004-2007) Master of Engineering (Biomedical Engineering)
HOME ADDRESS	9/1 Koh Klang Rd, Nong Hoi Muang, Chiang Mai E-mail: tchankong@gmail.com