THE DIABETIC PATIENT SOFTWARE AGENT

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ABSTRACT

The purpose of this thesis is to develop an agent-based simulation model of a diabetic patient's blood glucose levels in which the efficiency of various treatment strategies can be evaluated in a micro scope. A further aim is to establish a multi-agent system of evaluating the healthcare system response under various scenarios of healthcare policies in a macro scope. A framework is endeavoured to be constructed in order to extend its applications into other diseases.

The incidence of Type 2 diabetes mellitus is reaching epidemic proportions in the world in recent times. On one hand, the disease can result in various serious complications such as limb loss, blindness, ischemic heart disease and end-stage renal disease. On the other hand, people with diabetes can expect to live active, independent and vital lives if they try to keep their blood glucose in a target range through diabetes management strategies such as education, medication and lifestyle control. To quantitatively asses the efficiency of various treatment strategies, several cost-effective experiments in different simulation scenarios of treatment strategies are implemented in the proposed models *in silico* otherwise it is often not possible or too difficult, dangerous or unethical to do them *in vivo*.

Two individual patient agent models of a Controlled Patient Agent and a Self-Aware Patient Agent are presented. The author extends the original seminal work of Ackerman et al. of a mathematical model of the human glucose regulatory system and incorporates the enhanced model in the Controlled Patient Agent. The Self-Aware Patient Agent is enhanced based on the Controlled Patient Agent by introducing a blood glucose sensor *in silico* and a reasoning model of responding to the measures.

Furthermore, the signal technique of calculating a cross-correlation function and average blood glucose deviation between the continuous blood glucose and the interpolation of samples is proposed to evaluate blood glucose monitoring frequency in the Self-aware Patient Agent model.

A design of a multi-agent system is finally presented by introducing other healthcare components so that more interesting insights such as the healthcare quality, cost and performance can be observed in a macro scope.

The major observations from the experiments illustrated that the two agent models could represent typical diabetic patients. The agent models evaluate the efficiency of various lifestyles, the self-awareness and the treatment of self monitoring blood glucose in a quantitative way. This can help patients explore their prognosis if they are not meticulous in controlling their blood glucose levels and can assist patients to determine an optimal frequency for monitoring their blood glucose in order to reduce discomfort, cost and potential infection caused by intensity of measurement. By analyzing the simulation results, a base line of treatment strategies *in silico* is built, which may aid people to discover a personalized management regimen based on their situation.

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DEDICATIONS

To,

My respected parents, Yanzhong Wang and Xiaoxiang Ma,

My respected parents-in-law, Runbao Liu and Yuying Geng

My dear brother,Yuefeng Wang

My beloved wife, Ye Liu

My angelic baby daughter, Carolyn Wang

TABLE OF CONTENTS

ABSTRACT i

ACKNOWLEDGEMENTS iii

DEDICATIONS iv

TABLE OF CONTENTS v

LIST OF TABLES x

LIST OF FIGURES xi

ACRONYMS xiv

CHAPTER 1 INTRODUCTION 1

1.1 Overview of diabetes 1

1.1.1 The prevalence and costs of diabetes 1

1.1.2 Diabetes classifications 2

1.1.3 Type 2 diabetes treatments 3

1.2 Proposed models and methods 4

1.2.1 Controlled patient agent 4

1.2.2 Self-aware patient agent 5

1.2.3 Blood glucose monitoring frequency evaluation 5

1.2.4 Multi-agent system 6

1.3 Motivations and objectives 7

1.4 Contributions 8

1.5 Thesis organization 9

CHAPTER 2 LITERATURE REVIEW 10

2.1 Software agents 11

2.1.1 Basic concepts 11

2.1.2 Agent classification 12

2.1.3 Mobile agents 14

2.1.4 Multi-agent systems 15

2.1.5 TEEMA agent platform 16

2.2 Agent-based simulation in healthcare 17

2.3 Diabetes models 17

2.4 Related applications and systems review 19

2.4.1 Multi-agent system application in diabetic healthcare 19

2.4.2 Emergency department workflow simulation 20

2.4.3 Agent-based simulation framework 22

2.4.4 A Pre- and Type 2 diabetes simulator 23

2.4.5 Type 1 diabetes simulator 24

2.4.6 Model of the human glucose-insulin regulatory system 26

2.5 Summary 27

CHAPTER 3 CONTROLLED PATIENT AGENT MODEL 28

3.1 Method 28
3.1.1 Controlled patient agent model architecture 28
3.1.1.1 Ackerman model 29
3.1.1.2 Random walk model 32
3.1.2 Control patient agent model and algorithm 35
3.1.3 Assumptions in the model 41
3.1.4 User interface 41
3.2 Experiments and results 43
3.2.1 Experiment configurations 43
3.2.2 Recommended blood glucose range for diabetic patients 45
3.2.3 Experimental results 45
3.3 Summary 51
CHAPTER 4 SELF-AWARE PATIENT AGENT MODEL 53
4.1 Self monitoring blood glucose 53
4.2 Method 54
4.2.1 Self-aware patient agent model architecture 54
4.2.2 Self-awareness 56
4.2.3 Self-aware patient agent algorithm 56
4.2.4 User interface 58
4.3 Experiments and results 58

4.3.1 Experiment configurations 58
4.3.2 Experimental results 61
4.4 Summary 67
CHAPTER 5 BLOOD GLUCOSE MONITORING FREQUENCY EVALUATION 68
5.1 Signal analysis techniques in diabetes physiology 68
5.2 Evaluation method 69
5.2.1 Blood glucose monitoring frequency 69
5.2.2 Self-aware patient agent categories 72
5.2.3 Interpolation of samples 73
5.2.3.1 Linear interpolation 73
5.2.3.2 Higher order polynomial interpolation 77
5.2.3.3 Comparison of linear and high order polynomial interpolation 80
5.2.4 Normalized cross-correlation at zero lag 81
5.2.5 Average value deviation 84
5.3 Experiments and results 86
5.3.1 Normalized cross-correlation at zero lag 86
5.3.2 Average deviation value 92
5.4 Summary 97
CHAPTER 6 THE MULTI-AGENT SYSTEM 102
6.1 System architecture 102

6.2 Agent description 106

6.2.1 Interface Agent 106

6.2.2 Administrative Agent 106

6.2.3 Report Agent 107

6.2.4 Patient Agent 107

6.2.5 Healthy Person Agent 108

6.2.6 Physician Agent 109

6.2.7 Ward agents 109

6.2.8 Emergency Agent 110

CHAPTER 7 CONCLUSIONS AND FUTURE WORKS 111

REFERENCES 115

LIST OF TABLES

Table 3-1 Eleven scenarios in the experiments..... 44

Table 3-2 Summary blood glucose information of the controlled patient agent 46

Table 3-3 Times over thresholds of the controlled patient agent..... 46

Table 4-1 Configurations of self-awareness of the self-aware patient agent..... 60

Table 4-2 Coefficients of parameter adjustment in the Ackerman model..... 60

Table 4-3 Summary blood glucose information of self-aware patient agent..... 61

Table 4-4 Times over thresholds of the self-aware patient agent 62

Table 5-1Samples and monitoring time in a simulation example..... 78

Table 5-2 Piecewise cubic Hermite interpolating polynomial coefficients..... 79

Table 5-3 Comparison between linear and high order polynomial interpolation in the Healthy & Young SPA model..... 80

Table 5-4 Comparison between linear and high order polynomial interpolation in the Sick & Elderly SPA model 80

Table 5-5 NCCZLs of the Sick & Elderly SPA in six-day simulation scenario..... 83

Table 5-6 AVDs of the Sick & Elderly SPA in six-day simulation scenario 85

Table 5-7 Various calculations of NCCZLs with different MFs in 30 days..... 88

Table 5-8 Various calculations of AVDs with different MFs in 30 days 93

Table 5-9 Thresholds of mean and variance of NCCZLs and AVDS 97

Table 5-10 Evaluation table..... 101

Table 6-1 Persons with diabetes in Saskatchewan..... 108

LIST OF FIGURES

Figure 2-1 A part view of an agent typology [26] 13

Figure 3-1 Controlled patient agent architecture 28

Figure 3-2 Ackerman model simulation results 31

Figure 3-3: RW model simulation results 34

Figure 3-4 (a) Profiles of plasma glucose and insulin (b) Actual human blood glucose trace 34

Figure 3-5 Controlled patient agent flowchart 38

Figure 3-6 (a) Controlled patient agent single-day simulation results (b) Controlled patient agent multi-day simulation results 40

Figure 3-7 CPA single-day simulation results with incorporating stochastic nature of metabolic 40

Figure 3-8 User interface of patient agent for general configurations 42

Figure 3-9 User interface of patient agent for lifestyle manipulation 42

Figure 3-10 Times over thresholds of controlled patient agent 47

Figure 3-11 (a) Daily blood glucose in 3D format (b) Daily blood glucose range (controlled patient agent in the scenario without intervention) 49

Figure 3-12 Daily blood glucose in 3D format (b) Daily blood glucose range (controlled patient agent in the scenario with morning exercise) 49

Figure 3-13 Daily blood glucose in 3D format (b) Daily blood glucose range (controlled patient agent in the scenario with controlled breakfast diet) 50

Figure 3-14: (a) Daily blood glucose in 3D format (b) Daily blood glucose range (controlled patient agent in the scenario with controlled eating time and diet) 50

Figure 4-1 Self-aware patient agent architecture 55
Figure 4-2 Self-aware patient agent flowchart..... 57
Figure 4-3 Times over thresholds of the self-aware patient agent..... 62
Figure 4-4 (a) Daily blood glucose in 3D format (b) Daily blood glucose range (self-aware patient agent in the scenario without intervention) 64
Figure 4-5 Daily blood glucose in 3D format (b) Daily blood glucose range (self-aware patient agent in the scenario with morning exercise)..... 64
Figure 4-6 Daily blood glucose in 3D format (b) Daily blood glucose range (self-aware patient agent in the scenario with controlled breakfast diet)..... 65
Figure 4-7 (a) Daily blood glucose in 3D format (b) Daily blood glucose range (self-aware patient agent in the scenario with controlled eating time and diet)..... 65
Figure 4-8 Results comparison in times of over 15 mmol/L 66
Figure 5-1 Samples with monitoring frequency of (a) 6 times/day (b) 3 times/day (c) 1 time/day (d) 1 time/week 70
Figure 5-2 The Healthy & Young SPA's continuous blood glucose, linear interpolation and samples with monitoring frequency of (a) 6 times/day (b) 3 times/day (c) 1 time/day (d) 1 time/week 75
Figure 5-3 The Sick & Elderly SPA's continuous blood glucose, linear interpolation and samples with monitoring frequency of (a) 6 times/day (b) 3 times/day (c) 1 time/day (d) 1 time/week 76
Figure 5-4 The Healthy & Young SPA's continuous blood glucose, high order polynomial interpolation and samples with monitoring frequency of (a) 6 times/day (b) 3 times/day (c) 1 time/day (d) 1 time/week 78

Figure 5-5 The Sick & Elderly SPA's continuous blood glucose, high order polynomial interpolation and samples with monitoring frequency of (a) 6 times/day (b) 3 times/day (c) 1 time/day (d) 1 time/week 79
Figure 5-6 NCCZL of the Sick & Elderly SPA with monitoring frequency of 3 times/day 83
Figure 5-7 AVD of the Sick & Elderly SPA with monitoring frequency of 3 times/day. 85
Figure 5-8 Mean of the NCCZLs 89
Figure 5-9 Variances of the NCCZLs 89
Figure 5-10 Mean of NCCZLs with the MF of 6 times/day 90
Figure 5-11 Mean of NCCZLs with the MF of 3 times/day 90
Figure 5-12 Mean of NCCZLs with the MF of 1 time/day 91
Figure 5-13 Mean of NCCZLs with the MF of 1 time/week 91
Figure 5-14 Mean of AVDs 94
Figure 5-15 Variance of AVDs 94
Figure 5-16 Mean of AVDs with the MF of 6 times/day 95
Figure 5-17 Mean of AVDs with the MF of 3 times/day 95
Figure 5-18 Mean of AVDs with the MF of 1 time/day 96
Figure 5-19 Mean of AVDs with the MF of 1 time/week 96
Figure 5-20 Mark lines of thresholds of (a) Mean of the NCCZLs (b) Variances of the NCCZLs (c) Mean of the AVDs (d) Variances of the AVDs 99
Figure 6-1 Architecture of the multi-agent system 105

ACRONYMS

CPA	:	Controlled Patient Agent
SPA	:	Self-aware Patient Agent
MAS	:	Multi-Agent System
WHO	:	World Health Organization
ADA	:	American Diabetes Association
CDA	:	Canadian Diabetes Association
PDA	:	Personal Digital Assistant
TEEMA	:	TRlabs Execution Environment for Mobil Agents
AEE	:	Agent Execution Environment
DAI	:	Distributed Artificial Intelligence
GUI	:	Graphical User Interface
WAN	:	Wide Area Network
WWW	:	World Wide Web
GTT	:	Glucose Tolerance Test
RW	:	Random Walk
SMBG	:	Self Monitoring Blood Glucose
RCT	:	Randomized Controlled Trial
CBG	:	Continuous Blood Glucose
DES	:	Discrete Event Simulation
MCS	:	Monte Carlo Simulation
SD	:	System Dynamic
ABS	:	Agent-Based Simulation

FDA	:	Food and Drug Administration
CU	:	Control Unit
ED	:	Emergency Department
COPD	:	Chronic Obstructive Pulmonary Disease
CGM	:	Continuous Glucose Monitoring
s.c.	:	subcutaneous
BG	:	Blood Glucose
GI	:	Glycemic Index
NCCZL	:	Normalized Cross-Correlation at Zero Lag
AVD	:	Average Value Deviation
MF	:	Monitoring Frequency
PCHIP	:	Piecewise Cubic Hermite Interpolating Polynomial

CHAPTER 1

INTRODUCTION

The control of diabetes has become an interdisciplinary endeavor. Health care systems and providers are struggling to deliver the appropriate and necessary health care and support for patients as the plethora of diabetes-related symptoms of this illness are manifested in the afflicted population [1].

This thesis work presents two models of diabetic patient blood glucose levels in mobile agent environment: a Controlled Patient Agent (CPA) and a Self-aware Patient Agent (SPA). We then propose an application of a signal processing technique to evaluate blood glucose monitoring frequencies. A Multi-Agent System (MAS) architecture is also proposed to model the healthcare system.

In this chapter, an overview of diabetes is provided. The proposed models and methods are also briefly introduced.

1.1 Overview of diabetes

Diabetes is a common metabolic disorder featuring chronic hyperglycemia that results in microvascular and macrovascular complications [2-5]. It occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces [6].

1.1.1 The prevalence and costs of diabetes

According to the World Health Organization (WHO), more than 220 million people worldwide have diabetes. In 2004, an estimated 3.4 million people died from

consequences of high blood sugar, and WHO projects that this number will double between 2005 and 2030. Also, diabetes and its complications have a significant economic impact on individuals, families, health systems and countries. For example, WHO estimates that, in the period 2006-2015, China will lose $558 billion in foregone national income due to heart disease, stroke and diabetes alone.

1.1.2 Diabetes classifications

The classification of diabetes includes the following four clinical classes [7, 8].

- **Type 1 diabetes:** Type 1 diabetes is characterized by an absolute lack of insulin. Although this type of diabetes found in all ages, it generally occurs in childhood and adolescence.
- **Type 2 diabetes:** Type 2 diabetes comprises diseases in which the pancreas does not produce enough insulin or the body does not effectively use the insulin that is produced. It usually occurs in adulthood, but increasing numbers of children in high-risk populations are being diagnosed.
- **Other specific types of diabetes:** Diabetes due to other causes, e.g., genetic defects in β-cell function, genetic defects in insulin action, or diseases of the exocrine pancreas, drug or chemical induced.
- **Gestational diabetes:** Gestational diabetes temporarily occurs during pregnancy (usually after the 28th week of pregnancy). It influences approximately 2 to 4 per cent of all pregnancies (in the non-Aboriginal population) and involves an increased risk of developing diabetes for both mother and child.

This work focuses on Type 2 diabetes, since it comprises 90% of people with diabetes around the world, and is largely the result of excess body weight and physical inactivity [6].

1.1.3 Type 2 diabetes treatments

Type 2 diabetes can result in various serious complications such as limb loss, blindness, ischemic heart disease and end-stage renal disease [5]. However, people with diabetes can expect to live active, independent and vital lives if they try to keep their blood glucose (BG) in a target range through careful diabetes management strategies, which include the following [4]:

- **Education:** Diabetes education is a paramount first step. All people with diabetes need to be aware of their condition and its complications. For instance, the American Diabetes Association (ADA) recommends an at least annual assessment of self-management skills and knowledge of diabetes as well as the provision or encouragement of continuing diabetes education [9].
- **Physical activity:** Regular physical activity, such as aerobic exercises and light resistance exercises, helps to control BG levels, improves the body's sensitivity to insulin, and enhances overall fitness.
- **Nutrition:** What, when and how to eat all play an important role in regulating BG levels. Patients can regulate BG by eating food containing less carbohydrates that release glucose into bloodstream [10]. Keeping a regular food intake schedule also helps in the control of blood sugar levels, e.g., eating about the same amount of food at about the same time every day [11].

- **Medication:** Medication such as oral pills and/or insulin injections may be required to assist people control their BG levels more effectively.
- **Lifestyle management:** Obviously adopting a healthier lifestyle, such as restricting food consumption, improving physical activity and releasing life pressure, can help in improving fitness.

1.2 Proposed models and methods

1.2.1 Controlled patient agent

A patient agent represents a human diabetic patient or group of diabetic patients with similar lifestyles. The CPA integrates several essential attributes in diabetes management, such as eating habits, physical activity levels and medication.

The CPA incorporates the Ackerman model [12, 13] and the Random Walk (RW) model in a mobile agent environment. The Ackerman model is a mathematical model of the human glucose regulatory system, which has led to significant follow-on research. However, their work does not address the BG trace overnight. To simulate the BG levels in a 24-hour mode, we first extend the Ackerman model into nights by introducing the RW model. It is also enhanced by incorporating a random component of capturing stochastic human behaviours. The extended model is then incorporated into the CPA model. The name does not have a special meaning, but only comes from the comparison with the SPA, which is characterized by self-awareness. The CPA illustrates BG levels in different lifestyles that refer to diabetes treatments recommended by the Canadian Diabetes Association (CDA) as discussed in section 1.1.3. It demonstrates how the

patient's lifestyle can influence the control of BG by counting the number of times BG levels fall out of the target range.

1.2.2 Self-aware patient agent

Based on the CPA, the SPA further assimilates a BG sensor *in silico* and a reasoning model of changing behaviours, which is analogous to the human patient pricking his finger and using a drop of blood to measure his own blood glucose and then responding to the BG samples. It seems reasonable to expect that values which are out of the desired bounds would result in the human subject altering to some extent his own behaviour in terms of food intake, exercise, adherence to medications, etc. Experimental results demonstrate the effectiveness of self-awareness through comparisons between the CPA and the SPA.

1.2.3 Blood glucose monitoring frequency evaluation

Self Monitoring Blood Glucose (SMBG) can, theoretically, lead to better compliance with diet and exercise advice, and medication regimens, eventually resulting in better glycemic regulation [14]. Therefore, it is highly recommended for use by people with Type 2 diabetes [15, 16]. However, high intensity of monitoring leads to discomfort, potential infection and a financial burden, so it is increasingly necessary to investigate optimal frequencies. In addition, the frequency for using SMBG can vary according to the individual patient. The conventional way of Randomized Controlled Trial (RCT) *in vivo* has obvious disadvantages such as it being time consuming, the huge cost associated with it, and inherent difficulties in studying unique events.

Our method is to compare Continuous Blood Glucose (CBG) and interpolation of samples generated by the SPA to see how samples can represent the CBG. The similarity and average value deviation are the two factors to be considered. To have personally optimal frequencies, the SPA is categorized into nine types in terms of age levels and health status.

This method quantitatively assesses the capability of samples to present the CBG using four different monitoring frequencies. It intends to build a base line of monitoring frequency for different SPA *in silico,* which may assist people to determine an optimal frequency based on their situation.

1.2.4 Multi-agent system

A MAS is an admirable method to model the healthcare system of huge scale and enormous complexity, since the healthcare system can naturally be regarded as a collection of autonomous interacting components-agents. This thesis only gives the architecture design of the multi-agent system. Experiments and discussion will be the subject of future works.

The proposed multi-agent healthcare system has ten kinds of software agents: Interface Agent, Administrative Agent, Report Agent, Patient Agent, Healthy Person Agent, Physician Agent, Kidney/Dialysis Ward Agent, Eye Ward Agent, Heart/Stroke Ward Agent, Foot Ward Agent and Emergency Agent. Each agent represents a component of the healthcare system, for instance, the Patient Agent represents a group of human patients and the Physician Agent that has the knowledge-based reasoning model represents diabetes specialists. Through evaluating the interaction of these agents, the quality, cost and performance of healthcare can be observed.

1.3 Motivations and objectives

General motivations derive from the prevalence and costs of diabetes as mentioned in section 1.1.1. Type 2 diabetes can result in various serious complications such as limb loss, blindness, ischemic heart disease and end-stage renal disease [5]. Fortunately, people with diabetes can expect to live active, independent and vital lives if they try to keep their BG in a target range through careful diabetes management strategies such as education, medication and lifestyle management.

Cost-effective experiments in different simulation scenarios can be implemented in the CPA and the SPA models to assess the efficiency of various treatment strategies. For instance, simulation results can demonstrate the efficiency of a healthier lifestyle and self-awareness in a quantitative way, which can help patients to explore their prognosis if they are not meticulous in controlling their BG levels. Potential treatments including extreme situations can be conducted in the models, whereas it is often not possible or too difficult, dangerous or unethical to do them *in vivo*.

The motivation of blood glucose monitoring frequency evaluation is that SMBG is highly recommended for people with Type 2 diabetes [15, 16]. However, high intensity of monitoring leads to discomfort, potential infection and financial burden, so it is increasingly necessary to investigate optimal frequencies. The conventional way of RCT *in vivo* has obvious disadvantages such as it being time consuming, the huge cost associated with it and inherent difficulties in studying rare events.

The multi-agent system is an ideal method to model a healthcare system of huge scale and enormous complexity since the healthcare system can naturally be regarded as a

collection of autonomous interacting components-agents. A framework of the system has been developed, so that it can be extended into other diseases such as heart diseases.

The objectives are as follows.

- Develop patient agent models of the CPA and the SPA that can represent diabetic patients with similar conditions
- Quantitatively evaluate different diabetes treatment strategies such as lifestyle adjustment, self-management and SMBG
- Create a variety of patient agents to map the human population
- Present a novel method of evaluating blood glucose monitoring frequencies
- Build a multi-agent system to observe the response of the healthcare system in different policies
- Develop a framework of multi-agent system that can be extended into other diseases

1.4 Contributions

We list the thesis research contributions as follows.

- Our work extended the original seminal work of Ackerman model.
- We presented individual patient agent models of the CPA and the SPA in mobile agent environment in which cost effective experiments can be conducted *in silico* to quantitatively assess the effectiveness of various treatment strategies.
- The SPA model was personalized into nine categories in terms of age and health status to map the human population.
- The efficiency of SMBG was evaluated in the SPA model to investigate an optimal frequency of sampling.

- We quantitatively asses the capability of samples in terms of representing the CBG
- We proposed a design of a multi-agent system in order to observe in a macro scope interesting insights such as the quality, cost and performance of the healthcare.
- The proposed models and multi-agent system can be used in simulation studies for education, health care planning and health care policy development.
- A framework is endeavoured to be constructed in order to extend its applications to other diseases.

1.5 Thesis organization

This thesis is organized as follows: Chapter 2 is a literature review of software techniques, agent-based simulation in healthcare, diabetes models and related applications. Chapter 3 proposes the CPA model to simulate BG levels of diabetic patients with different lifestyles. The enhanced model of SPA that is capable of self monitoring its BG and acting to the measurements is proposed in Chapter 4. Based on the SPA, Chapter 5 presents a novel blood glucose monitoring frequency evaluation method. A design of a multi-agent architecture for modeling a healthcare system in diabetes is given in Chapter 6. Chapter 7 concludes the thesis research with future extensions.

CHAPTER 2

LITERATURE REVIEW

Over the years, healthcare requirements have grown increasingly and healthcare organizations have become larger, more complex and more costly as societies have become wealthier and medicine continues to improve [17-19]. The application of computer modeling and simulation has been a very successful method in solving healthcare problems. The application areas vary from risk analysis to medical decision making, and from health policy to health economics. Models have been built for the analysis of chronic diseases such as diabetes, HIV/AIDS, sexually transmitted diseases, cancer, and heart disease [20-22].

Computer simulation, or just simulation, is a decision support technique that enables stakeholders to conduct experiments with models that represent real-world systems of interest [23]. Simulation modeling in healthcare commonly incorporates random variations to represent certain key characteristics or behaviours. The applications in healthcare *in silico* are of considerable value, since it is often not possible or too difficult, dangerous or unethical to do them *in vivo*. Several different classifications of simulations have been conducted. Jun at al. classified them into two categories: management of patient flow and resource allocation [24]. Brailsford identified three main groups of models in terms of detail levels on which the models are focusing: at the human body level, at the healthcare unit level, and at the system-wide level [25]. Most recently, after reviewing healthcare simulation literatures that have been published between 1970 and 2007 in high-quality journals, Mustafee at al. identified four simulation techniques: Discrete Event Simulation (DES), Monte Carlo Simulation (MCS), System Dynamic (SD)

and Agent-Based Simulation (ABS) [19]. In this review, we have to limit our scope; thus we will only discuss ABS and diabetes models.

This chapter discusses the software agent technique and the ABS in healthcare, and then focuses on diabetes models. Subsequently, we present several related applications and systems on a more detailed level. A summary is given in the last section of this chapter.

2.1 Software agents

Software agent techniques have been implemented in an ever-increasing application space, from workflow management to data mining, from business process reengineering to Personal Digital Assistants (PDAs), and from education to bioengineering. This section will discuss the basic concept of the software agent and its classification as well as multi-agent systems. TRlabs Execution Environment for Mobile Agents (TEEMA) is also presented since it has been adopted as an Agent Execution Environment (AEE) in this work.

2.1.1 Basic concepts

The concept of an agent can be traced back to the early days of research into the field of Distributed Artificial Intelligence (DAI) in the 1970s, which include Carl Hewitt's concurrent Actor model [26]. In this model, Hewitt proposed a term of 'actor', which proposes the concept of a self-contained, interactive and concurrently-executing software object. An actor has an encapsulated internal state, a mail address and behaviour, and can also communicate with other actors by messaging [27].

It is very difficult to precisely define an agent. Even within the software affiliation, the word ‘agent’ is really an umbrella term for a variety of research and development [26]. The response to this lack of definition is that some agent researchers have invented many synonyms such as softbots (software robot), personal agents and autonomous agents [26]. Nonetheless, we try to propose one definition here to make an agent clear to the audience. “An agent is referred to a component of software and/or hardware which is capable of acting exactingly in order to accomplish tasks on behalf of its user [26].” Additionally, commonly acceptable concepts of software agents are listed as follows [26, 28, 29]:

- **Autonomy:** Agents operate without the direct intervention of humans or others, and have some kind of control over their actions and internal state [30].
- **Social Ability/Cooperation:** Agents interact with other agents (and possibly humans) via some kind of agent-communication language [31].
- **Reactivity/Proactivity:** agents perceive and respond to their environment in a timely fashion to adapt their behaviour accordingly. The environment may be the physical world, a user via a Graphical User Interface (GUI), a collection of other agents, the Internet, or perhaps even all of these combined.
- **Learn:** Agents would have to learn as they react and/or communicate with their peers and their environment.

2.1.2 Agent classification

Software agents are difficult to define, as demonstrated, and similarly complicated to categorize. According to the overview work of Nwana [26], there are numerous ways to classify existing software agents.

Firstly, agents can be classified by their mobility: for instance, the ability the agent to move around networks. Thus, agents can be categorized into the classes of either static or mobile agents.

Secondly, they may be classified in terms of either deliberative or reactive agents. Deliberative agents derive from the deliberative thinking paradigm in which the agents have an internal symbolic, reasoning model, and these agents communicate and negotiate with other agents to achieve coordination. By contrast, reactive agents do not have any internal, symbolic models of their environment, and they behave using a stimulus/response type of action by responding to the present state of the existing environment [32].

Thirdly, agents may be categorized based on several ideal and primary attributes which agents should exhibit. Nwana et al. identified three attributes: autonomy, learning and cooperation, instead of the four we list in section 2.1.1, since they believe that reactivity is a learning method. Nonetheless, they use these three attributes classify agents as collaborative agents, collaborative learning agents, interface agents and truly smart agents (Figure 2-1). Truly smart agents, however, have not yet been developed. As Maes notes, "current commercially available agents barely justify the name" [33]. Foner is even more emphatic [34].

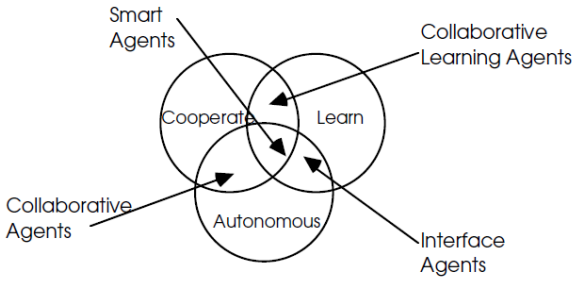


Figure 2-1 A part view of an agent typology [26]

Fourthly, agents can also be classified by other characteristics, i.e. roles, or any combination of two or more attributes.

Nwana finally classified software agents into seven types to cover most currently existing agents: collaborative agents, interface agents, mobile agents, information/Internet agents, reactive agents, hybrid agents, and smart agents [26].

We will discuss mobile agents in the next section, as the technique that we use in this work follows in this typology.

2.1.3 Mobile agents

Mobile agents are computational software processes accomplished by roaming Wide Area Networks (WANs) such as the World Wide Web (WWW), communicating with other types of hosts, accumulating information on behalf of its owner and coming 'back home' having achieved the duties set by its user [26]. However, not all agents are mobile and mobility does not guarantee an agent [35]. Mobile agents are agents, since they possess at least one of the concepts listed in section 2.1.1.

The key point of mobile agents is that agents need not be stationary. An agent can just stay in one place and interact with its environment through conventional means, such as remote procedure calling and messaging [35]. We call these agents stationary agents. A mobile agent, by contrast, is not bound to the system on which it executes [36]. The idea is that mobility in agent can provide significant benefits in certain applications in comparing to their stationary counterparts. The benefits of mobility are identified as a number of practical advantages [26, 35].

- **Reduced communication costs:** Transferring only useful information instead of raw data can be very time-efficient and will save cost bandwidth.

- **Overcoming limited local resources:** Mobile agents are capable of using other machines that have more processing power and storage than local counterparts.
- **Easier coordination:** Collating all the results locally can be simpler to coordinate a number of remote and independent requests.
- **Asynchronous computing:** Mobile agents may be 'set off' when you can do something else and come back later. They may also perform in other machines offline.
- **A flexible distributed computing architecture:** Mobile agents offer an innovative way of doing distributed computation which functions differently from static set-ups.
- **Dynamic adaption:** Mobile agents can react autonomously to changes by sensing their execution environment. Multiple mobile agents possess unique capabilities of distributing themselves among a complex architecture to maintain the optimal configuration for solving a particular problem.

As discussed, mobile agents can travel around networks and interact with other agents; therefore, in most cases, they embed in a MAS.

2.1.4 Multi-agent systems

MAS are a body of multiple autonomous agents that interact, cooperate, and negotiate with each other in order to satisfy their design objectives [37-39]. Two main characteristics can be derived from the definition. Firstly, each agent is autonomous and is able to solve the problem in its domain. However, it only has incomplete information or limited capabilities for solving the whole problem and, thus, has a limited viewpoint. Secondly, through agent interaction, the system can conduct a complex problem that is

beyond the capability of individual agents. Furthermore, the interaction here can be either cooperation or competition/negotiation.

If a problem domain is especially complex, huge, or/and unpredictable (i.e. modeling of the healthcare system), then the only way it can reasonably be addressed is to develop a number of functionally specific agents that are specialized for solving a specific problem aspect. For instance, it is impossible to simulate the healthcare system in a single model because of its large scale and enormous complexity. An ideal alternative is to model each individual component of the system, such as a patient, a physician, and a hospital ward, instead of the whole healthcare system. Through observing the interaction of these components, the system response can be evaluated. The advantages of this method are obvious, as discussed previously.

2.1.5 TEEMA agent platform

To execute agents, they need an AEE or a platform. This is a software system that provides a runtime system for agents to execute and a standard interface for interactions, services for creation, migration and termination of mobile agents, and supports agent mobility and communication while providing security for both hosts and agents [40].

TEEMA is such an AEE and was adopted as the platform in this work because of its availability and its familiarity to us. It has been developed in Java jointly by TRLabs Regina and the University of Regina. Just like any other AEE, TEEMA provides standard libraries to support various types of operations for agents such as addressing, naming, messaging, mobility, security and logging [40, 41]. TEEMA also supports a multi-agent system and provides multitasking services.

2.2 Agent-based simulation in healthcare

ABS is a relatively new approach of modeling systems consisting of autonomous and interacting agents. A growing number of agent-based applications, most of which are MAS, have been developed to deal with many different types of problems in the health care domain. Such applications can be found in areas such as patient scheduling, community care, organ and tissue transplant, information access, decision support systems, training, internal hospital tasks, senior citizen care etc. [42].

This area draws the attention of researchers due to its many advantages. Firstly, ABS allows people to explicitly model the complexity inherent in the healthcare system arising from individual actions and interactions in the system, which is either not possible or not readily accommodated utilizing traditional modeling techniques, such as DES or SD [43]. The second advantage of ABS is that it enables the interconnection and interoperation of multiple existing legacy systems. It also provides solutions that efficiently utilize distributed information and expertise. Another advantage comes from distributed computing such as computational efficiency, reliability and maintainability.

2.3 Diabetes models

In this section, we focus on models of the glucose-insulin regulatory system. These models are capable of simulating the glucose-insulin system in diabetes; therefore cost-effective experiments in different simulation scenarios can be implemented *in silico* to assess the efficiency of various treatment strategies.

The history of this line of research can be traced back to the 1960s when Ackerman at al. proposed a mathematical model of the glucose-tolerance test and blood glucose regulation [12, 13]. Their aim was to increase the understanding of normal and

abnormal glucose regulation. Ackerman's work has led to significant follow-up research including the study of Jansson et al. in which Ackerman's model was used to analyse the BG curves obtained during Oral Glucose Tolerance Test in 378 cases. The mathematical model estimates the rate of intestinal glucose resorption, and was used to significantly improve the distinction between diabetes mellitus and the normal state. Following that, Wu [44] used Ackerman's model to evaluate the degree of diabetes in a particular subject and this subject's response to medications. Wu attempted to define the effect of the medication in terms of parameter fitting of blood glucose measured from a diabetic subject with or without medication. He attempted to assess the impact of the medication based on the values of the parameters in Ackerman's model. The most recent research following up the Ackerman model is proposed by Shiang [45] in 2010. Their study aims to develop methods to interpret laboratory glucose and insulin data from glucose tolerance test, as well as enhance the Ackerman model.

Glucose insulin simulators either in a whole body level [46-48] or in a organ/cellular-level [49, 50] can also be found in this research area. For instance, the efficacy of several drug treatments could be evaluated in a pre-diabetes and Type 2 diabetes simulator [47]. A milestone in this line of research is a Type 1 diabetes simulator developed by Kovatchev at al. [48], which is the first model-based simulator of the human metabolism system accepted by the Food and Drug Administration (FDA) as a viable tool for the preclinical testing of control algorithms prior to animal trials.

2.4 Related applications and systems review

2.4.1 Multi-agent system application in diabetic healthcare

In this study, Zhang at al. [51] propose a multi-agent platform to solve problems in a children's diabetic healthcare setting. The platform focuses on improving the collaboration of stakeholders and on supporting decision making.

Two main characteristics of children's diabetes management are described: the distribution of patients and the level of multi-care involved. Patients are distributed everywhere while care-providers do not often work together. This leads to two difficulties, which are communication and intelligent decision support problems. For instance, patients have to contact the doctors or nurses by phone, and often fail to provide sufficient information for these doctors and nurses to make decisions.

The authors, therefore, develop a MAS to cope with the aforementioned problems. The system features real time glucose monitoring and management, intelligent decision supports and user task delegation. The Gaia is selected as agent development methodology and JADE is adopted as an AEE. It is assumed that each agent has a corresponding human user in the real world. Human users can control their agents in acute situations, but the agents can also work automatically. These agents work on multi-platforms, such as PCs, laptops and smart phones.

After doing field studies, the authors identify specifications and define functionalities of the system as follows:

- receives data from medical devices and sends alarms to the corresponding agents/users when necessary,
- automatically organizes meetings for users, and

- decomposes predefined tasks and delegates sub-tasks to other agents/users.

Each agent may offer one or more services at the same time. The services include Patient Manager, Patient Alarm, Alarm Receiver, Meeting Manager, Meeting Responder, Task Manager and Task Handler. Four types of agent roles are designed to map human users in real world, namely, PatientAgent, ParentAgent, HospitalStaffAgent and SchoolNurseAgent.

Patients can use a Patient Control Panel that is able to run on Windows Mobile, a Java-supported mobile or stationary PC. It aids patients to record their activities related to diabetes. The real-time monitoring function is provided by the use of software agents. The system also provides decision support of diagnosis and information for care-providers. The other functionality is meeting arrangement. Agents propose a meeting in details and communicate with their human actors and other agents to produce a reasonable meeting configuration.

The benefits the diabetic healthcare gains from the system are mainly 1) a formal communication channel for all human actors, and 2) avoiding unnecessary visits to the medical staff. In the future, according the authors, Control Units (CU) and Knowledge Base (KB) will be designed in detail. Specifically, the KB will be enriched to map the real world in a more realistic way. Also, stored knowledge should be in better correspondence with the CU, so that agents can make decisions more effectively.

2.4.2 Emergency department workflow simulation

In this research, Wang [52] presents an agent-based simulation to model several phases in the Emergency Department (ED) workflow. The general objective of the study is to present an agent-based simulation method of evaluating ED in different settings. The

specific purpose is to characterize and study the ED performance under various settings of the triage process and radiology procedure process. The author analyzes two simulated cases to illustrate the effectiveness of changing the triage process and the radiology process in terms of the patient throughout time and the other critical performance measures. According to the findings, the author believes that this study can be used to plan alternations, identify bottlenecks, and study the non-linear relationships among various phases in the ED workflow.

The phases in the workflow are identified as patient arrival, triage process, nurse screen, physician examination, radiology procedure, and result review and disposition. The waiting time can be counted among the phases.

Patients and healthcare providers are modeled by their corresponding agents such as patient agents, triage nurse agents, bedside nurse agents, physician agents, and radiologist agents. Simple rules and appearance are assigned to the agents. For example, patient agents are designated by a yellow “sad face”. The color changes according to their status.

As system input information, four types of workflow configuration can be adjusted, which are patient arrival characteristics, triage characteristics, nurse care characteristics, physician care characteristics and radiology order characteristics. The output information is patient throughout time from which the ED performance is observed.

This ABS provides a convenient tool for users in ED to understand the workflow and evaluate the impact of potential changes. By tailoring the input parameters based on a specific ED condition, administers can observe the interaction among various individual

processes and the non-linear relationship between the change in one individual process and the change in the overall performance. One of the limitations of the study is that the behaviours of agents are specified by simple rules. However, this can be enhanced by introducing complex mathematical models.

2.4.3 Agent-based simulation framework

Charfeddine and Montreuil [53] develop a framework to integrate agent-based modeling and simulations of the population with a specific chronic disease in a large region and the healthcare system providing relevant services for this population. They present two agent-based models: the population model and the healthcare delivery network model. In the former model, potential patients are represented by software agents that integrate a stochastic modeling of health status. The evolution of health status generates healthcare service demand and its frequency. The later model is used to simulate the organizations and functions of the healthcare delivery network. The framework implemented is based on the Chronic Obstructive Pulmonary Disease (COPD) population and the healthcare delivery network of Canada.

The authors believe that healthcare demands can be more effectively simulated through agent-based stochastic modeling of the evolution of state of health of each person in a population of potential and actual patients. Each person is modeled by a number of individual factors such as socio-demographics, organic systems/clinical characteristics representing his/her health state, capabilities and lifestyle/behaviours. Four main population levels with different levels of demand are defined: general population, vulnerable population, affected population and registered population. The healthcare delivery network model is simulated by several agents, such as a patient agent, a care

provider agent, an access agent, a referring agent, a healthcare service agent and a healthcare center agent.

Obviously, the efficiency of the healthcare delivery system, costs of services and population characteristics, behaviour and disease specificities can influence the manner in which people consume the services, and vice versa. Integrating the population model and the healthcare delivery network model makes it possible to observe the impact of patients' behaviour and disease progression on their consumption of healthcare services. Also, it can be used to reflect the impact of the performance of the healthcare delivery network on the way patients use the offered services and on their state of health.

An agent-oriented simulation prototype for the case of the COPD model in Quebec's capital region is developed to illustrate the proposed integrated framework. Various statistics such as population distribution (by age, sex, zone, etc.) and the distribution of COPD patients by stage of disease severity are visualized in the user interface, which are dynamically generated on the simulated population. Different scenarios of network deployment, resource allocation and population projections can be evaluated.

2.4.4 A Pre- and Type 2 diabetes simulator

The pre- and Type 2 diabetes simulator developed by Dalla Man and Cobelli [47] can generate a number of virtual subjects through which the efficacy of various diabetes therapies can be assessed quickly by the means of cost-effective *in silico* experiments.

The model is comprised of twelve ordinary differential equations and twenty-six parameters that describe glucose and insulin kinetics, endogenous glucose production, meal rate of appearance, insulin secretion and renal excretion. A triple tracer meal

protocol database, derived from thirty-five pre-diabetic and twenty-three Type 2 diabetic patients, is available to construct the simulator model identification. The model is analyzed in each subject through subsystem decomposition and forcing function strategy. The individual parameter estimates are then used to reconstruct the joint parameter distribution in each population. Therefore, the simulator is able to realistically illustrate both population averages and inter-subject variability examined during clinical trials by incorporating pharmacokinetics/pharmacodynamics of major drugs such as metformin, DDP4 inhibitors and insulin.

2.4.5 Type 1 diabetes simulator

The motivations of the Type 1 diabetes simulator *in silico* proposed by Kovatchev et al. [48] come from the increasing interest of linking Continuous Glucose Monitoring (CGM) with subcutaneous (s.c.) insulin delivery.

The control algorithms in the system presented in this study for *in silico* testing have three principal components: "(1) a large cohort of n = 300 simulated 'subjects' (n = 100 adults, 100 adolescents, and 100 children) based on real individuals' data and spanning the observed variability of key metabolic parameters in the general population of people with Type 1 diabetes; (2) a simulator of CGM sensor errors representative of Freestyle Navigator™, Guardian RT, or Dexcom™ STS™, 7-day sensor; and (3) a simulator of discrete s.c. insulin delivery via OmniPod Insulin Management System or Deltec Cozmo® insulin pump." These three components construct a closed-loop control system. These components facilitate comprehensive computer-simulation testing of closed-loop control, through which performance of control algorithms with various

testing scenarios can be investigated cost-effectively prior to their clinical implementation.

The glucose–insulin meal model of Dalla Man and Cobelli [46, 54] provides the foundation for the simulation environment of *in silico* subjects. The glucose and insulin subsystems are assumed to be linked by the control of insulin on glucose utilization and endogenous production. The glucose subsystem is comprised of a two-compartment model of glucose kinetics. The insulin subsystem also has two compartments representative of a liver and plasma, respectively. Endogenous glucose production, glucose rate of appearance and glucose utilization are described in detail in the paper. The model has twenty-six free parameters. Hepatic and peripheral insulin sensitivity are the most two important ones. Subjects *in silico* that simulate diabetes observations such as glucose and insulin traces are created by a set of equations with parameters observed in Type 1 diabetes.

The *in silico* sensor is designed based on analysis of sensor errors that are representative of CGM challenges in terms of sensitivity, stability, calibration and the physiological time lag between blood and interstitial glucose concentration.

The *in silico* insulin pump is developed to simulate s.c. insulin delivery in terms of time and dynamics of insulin transport from s.c. tissue into blood and discrete insulin infusion corresponding to stepwise basal pump rate and insulin boluses.

The proposed components are implemented into a simulation platform using Simulink®. Within the simulation environment, several methods of glucose control are implemented. Measures of various treatments are observed, including several measures of average glycemia, temporal glucose variability, and associated risks for hypoglycemia

and hyperglycemia. Several experimental results are presented in the paper to illustrate the use of the simulation environment.

This computer simulation environment has been accepted by the FDA as a substitute for animal trials in preclinical closed-loop control experiments.

2.4.6 Model of the human glucose-insulin regulatory system

Shiang and Kandeel [45] introduce a computational model of insulin secretion and glucose metabolism to aid the diagnosis of diabetes mellitus in clinical research. A system of ordinary differential equations, which involve four parameters describing the glucose-insulin regulatory system, are proposed to represent the time course of plasma glucose and insulin concentrations during GTT in physiological studies. The four parameters are described in the Ackerman model (Equation 3.4). Their study aims to develop methods to interpret laboratory glucose and insulin data from Glucose Tolerance Test (GTT), as well as enhance the Ackerman model.

The key parameters are estimated by minimizing the sum of squared residuals function, which quantitatively assesses the difference between theoretical model predictions and GTT's experimental observations. The proposed methods of estimation are perturbation search and multiple-shooting.

The results show that the simulated trajectory perfectly matched the experimental data points. Their model demonstrates that diabetes can be properly indicated by the estimated parameters, computed frequency and period values. The enhanced approach may assist clinicians safely evaluate the diagnostic conditions based on the estimated parameters and discover the transition nature of human metabolic mechanism from normal to impaired glucose tolerance.

2.5 Summary

After reviewing the research based software agents, on the ABS and on diabetes models, three gaps and barriers are identified.

1. Human behaviours, especially related patient choices, are absent from most existing research, and are of paramount importance in the treatment of diabetes.
2. Simple rules equipped in agents limit the performance of the entire system.
3. Only the multi-agent results are analyzed in most systems, and important individual agent outputs are usually ignored.

This research begins with the development of CPAs and SPAs that integrate the enhanced Ackerman model rather than simple rules. The mathematic model incorporates human lifestyles such as food consumption, meal schedule and exercise intensity; thus, these behaviours, as important components of diabetes management, can be evaluated in a micro scope. A multi-agent framework is designed by introducing other healthcare components such as a Physician Agent, an Emergency Agent and ward agents, to evaluate the healthcare system response under various scenarios of healthcare policies in a macro scope. This framework is not limited to modeling only diabetes.

CHAPTER 3

CONTROLLED PATIENT AGENT MODEL

In this work, a patient agent represents a human diabetic patient or a group of diabetic patients with similar lifestyles. The CPA integrates several essential attributes in diabetes management that may affect diabetes, such as eating habits, physical activity levels and medication. The name of the CPA does not have a special meaning, but only comes from comparison with the SPA, which is characterized by self-awareness.

This chapter provides the architecture and method of the CPA. Experiments and results are then given to evaluate different treatment strategies. A summary is provided at the end of this chapter.

3.1 Method

3.1.1 Controlled patient agent model architecture

Figure 3-1 shows the architecture of the CPA model. The CPA is capable of transferring variables including food consumption, intensity of exercise and medication, and meal taking time, into BG levels. This model integrates the Ackerman model of simulating BG levels in the daytime and the RW model of controlling BG in the nighttime.

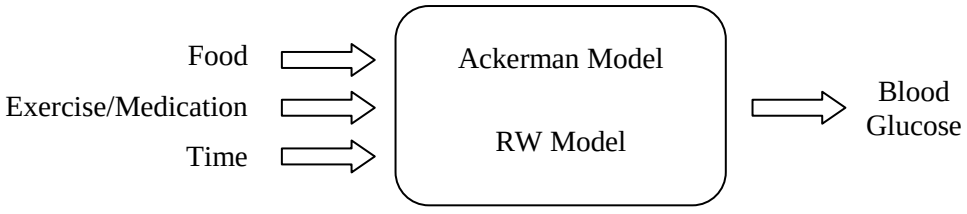


Figure 3-1 Controlled patient agent architecture

3.1.1.1 Ackerman model

The Ackerman model was proposed to characterize the human glucose regulatory system in the 1960s [12, 13]. The model is defined by the following differential equations:

$$\frac{dg}{dt} = -m_1 g - m_2 h + J \tag{3.1}$$

$$\frac{dh}{dt} = -m_3 h - m_4 g + K \tag{3.2}$$

where the coefficients m_i are positive constants, g and h are the concentration of glucose and hormone with t respectively. J is the rate of glucose infusion by intestines, and K is the rate of injection of H per unit blood volume. They are derived from the second order differential equation for g:

$$\frac{d_g^2}{dt^2} + 2\alpha\frac{dg}{dt} + \omega_0^2 g = S \tag{3.3}$$

where $= (m_1 + m_3)/2$, $\omega_0^2 = m_1 m_3 + m_2 m_4$, and $S(t) = m_3 J + \frac{dJ}{dt} + m_2 K$. In the case of $(t) = \frac{dJ}{dt} = R\delta(t)$, the solution has the form:

$$G = G_0 + \frac{R}{\omega} e^{-\alpha t} \sin \omega t \tag{3.4}$$

Wu [44] uses the Ackerman model to illustrate the possibility of devising an individual-based self-management regimen. Wu considers the postprandial BG excursion as a hormone-regulated, resilient system. According to Wu, the food intake can be treated as a bolus injection of glucose, which is represented as an impulse force *f(t).* The effects of exercises and hypoglycemic medication are lumped together as the damping factor, β. Using a second order differential equation to describe such an oscillatory system, i.e.,

$$\frac{d^2x(t)}{dt^2} + \beta\frac{dx(t)}{dt} + \omega_0 x(t) = f(t) \tag{3.5}$$

the post-prandial BG excursions can be determined. Wu defines:

$$x(t) = \frac{F}{\omega} e^{\frac{-\beta t}{2}} \sin \omega t \tag{3.6}$$

where x is the BG level as a function of time t, ω is the natural frequency of the system, β is measured based on the intensity of exercise and medication and F is a measure of food intake. Wu proposes that the three parameters in the model, F, ω, β, can not only reveal distinct characteristics between diabetic and non-diabetic individuals, but also provide guidelines to adjust one's lifestyle [44].

It should be noted that the Equation 3.4 and the Equation 3.6 have the same oscillatory pattern solution, and we eventually modify the Ackerman model as:

$$x(t) = G_0 + \frac{F}{\omega} e^{\frac{-\beta t}{2}} \sin \omega t \tag{3.7}$$

where G_0 is fasting blood glucose. The BG trace generated by the model is shown in Figure 3-2.

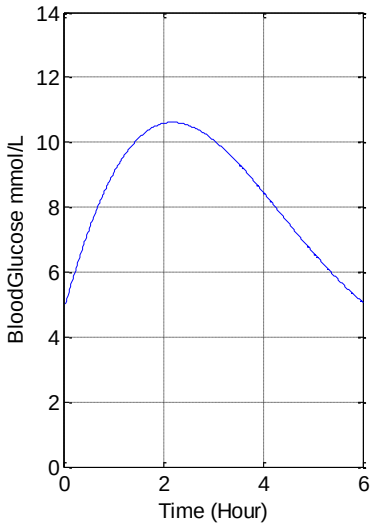


Figure 3-2 Ackerman model simulation results

Before integrating the Ackerman model into an ABS environment, we identify a number of limitations which we believe apply to all published blood glucose models [55]: (1) The model does not extend into the night, (2) The model does not incorporate any stochastic or unpredictable behaviour – which ultimately can be representative of human metabolic changes which are a response to daily life and living, (3) The model does not address the fact that human subjects are self-aware and respond to knowledge of their own condition. We cope with the former two limitations by developing the RW model of simulating BG overnight and incorporating a random number of capturing stochastic behaviours in the CPA. The third limitation is solved in the SPA, which is discussed in CHAPTER 4.

3.1.1.2 Random walk model

Extending the model to the nighttime is a very important issue since there are very often important changes in BG during the night. This feature has not been accounted for in any other models. While night metabolic rates vary dramatically and there are five established stages in sleep (Stage 1 - 4 and REM sleep) [56], we find that the BG does not correspond closely to these sleep stages. Instead, we consider three phases of sleep-based BG interaction: light sleep (gradual decrease in BG level), deep sleep (relatively flat low BG level), and preparing to wake up (abrupt steady increase in BG).

Three one-dimensional RWs are proposed to represent the three phases; therefore it is called a RW model. A RW is a mathematical formalization of a trajectory that consists of taking successive random steps [57]. The trajectory of a RW depends on two factors: one is the step size; and another is the distribution of the positive and negative steps. Equation 3.8 illustrates the RW model.

$$BG(t) = BG(t_3) + \sum_{t_3}^{t_{0N}} 0.02 \times G(p(t))$$

$$p(t) = \begin{cases} 0.4, & t_3 < t \leq t_4 \\ 0.5, & t_4 < t \leq t_5 \\ 0.6, & t_5 < t \leq t_{0N} \end{cases} \quad (3.8)$$

where $BG(t)$ is the blood glucose level and $G(p(t))$ is a random number +1 or −1. $p(t)$ is the possibility of $G(p(t))$ equaling +1. t_3 is the time of six hours after dinner has been eaten, when the Patient Agent is assumed to be going to sleep. t_4 and t_5 represent the start time of the second and third sleep phases, respectively. t_{0N} is the time breakfast is eaten the next day. Other critical times of t_0, t_1 and t_2 are defined in the Equation 3.12.

The first phase starts at 6 hours after dinner consumption and ends at 1:59am the next day. In this phase, the step size is defined as 0.02 mmol/L and the probability of a positive step is 40%. The second phase is from 2am to 6am where the step size is defined as 0.02 mmol/L and the probability of a positive step is 50%. The third phase is from 6:01am until when breakfast is eaten. The step size is defined as 0.02 mmol/L and the probability of a positive step is 60% in this phase. Figure 3-3 shows a possible presentation of the model. These three phases, in contrast to the stages of sleep, appear to be consistent with results presented in the Textbook of Diabetes (Figure 3-4(a)) [58] and actual human blood glucose monitored by CGM (Figure 3-4(b)).

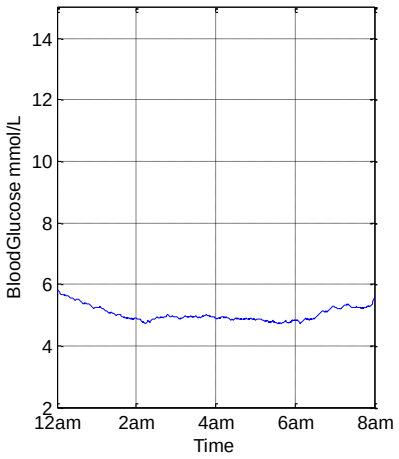
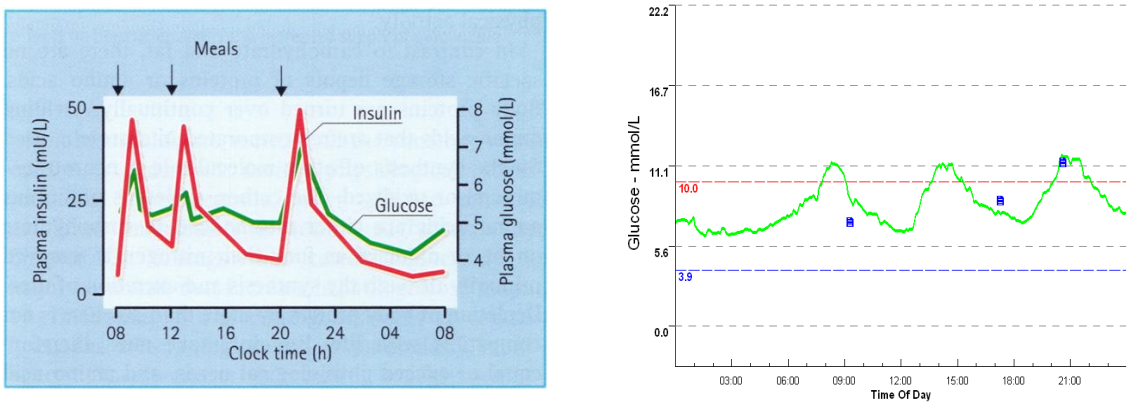


Figure 3-3: RW model simulation results



(a) (b)

Figure 3-4 (a) Profiles of plasma glucose and insulin (b) Actual human blood glucose trace

3.1.2 Control patient agent model and algorithm

The CPA algorithm of integrating the Ackerman model and the RW model is generally straightforward. Three no-overlap Ackerman models that represent three major meals simulate BG trajectory in the daytime while the three-phase RW model presents the BG trace overnight. Equations 3.9 ~ 3.12 illustrate the mathematical model of the CPA.

$$BG(t) = G_i + \frac{F}{\omega} e^{\frac{-\beta(t-T)}{2}} \sin \omega(t-T) + \sum_{t_3}^{t_{0N}} 0.02 \times G(p(t)) \tag{3.9}$$

$$G_i = \begin{cases} BG(t_0), & t_0 < t \leq t_1 \\ BG(t_1), & t_1 < t \leq t_2 \\ BG(t_2), & t_2 < t \leq t_3 \\ BG(t_3), & t_3 < t \leq t_{0N} \end{cases} \tag{3.10}$$

$$T = \begin{cases} 0, & t_0 < t \leq t_1 \\ t_1, & t_1 < t \leq t_2 \\ t_2, & t_2 < t \leq t_3 \\ t, & t_3 < t \leq t_{0N} \end{cases} \tag{3.11}$$

$$\begin{aligned} t_0 &= Rand(breakfast\ schedule\ window) \\ t_1 &= Rand(lunch\ schedule\ window) \\ t_2 &= Rand(dinner\ schedule\ window) \end{aligned} \tag{3.12}$$

where t_0, t_1 and t_2 are breakfast, lunch and dinner consumption times, respectively. t_4 and t_5 represent the start times of the second and third sleep phases respectively, and t_{0N} is the breakfast consumption time of the next day, which is defined in Equation 3.8.

Figure 3-5 shows the flowchart of the CPA. The system first received configurations from users. The corresponding parameters of *food consumption levels, food schedule range* and *intensity of exercise & medication* are *F*, *t* and β respectively in Equation 3.9. Glycemic Index (GI) is used as a measure of the food. GI is a numerical index with a scale of 0 to 100 that evaluates carbohydrates depending on their rate of glycemic response or their conversion to glucose within the human body [59]. Food with higher GI causes more rapid rise in blood sugar. The range of the value of β is from 0.0 to 1.0 with 1.0 representing the highest intensity workout and/or medication. The system randomly selects a time as *t* from a meal schedule window to mimic stochastic behaviours of human patient. ω is the system frequency of the patient agent model, and can present risk factors such as age, gender, ethnicity or health status. Its value defined from 0.46 to 0.84 [44]. The CPA model does not consider risk factors so ω is defined as an average value to generally represent a group of diabetic patients. We further add a component of random value to *food consumption levels*, *intensity of exercise & medication* and the system frequency of ω to allow them to be random within a certain range, which is representative of human responses to daily living. Thus the model is enhanced to allow interaction between meals and effects due to human activity to enter the model.

After the settings, the three non-overlap Ackerman models start to simulate BG trajectory for the daytime, when the major meals are consumed. The RW model takes

over to generate BG from six hours after dinner consumption until the time when breakfast is eaten the next day. The process repeats till the simulation is finished.

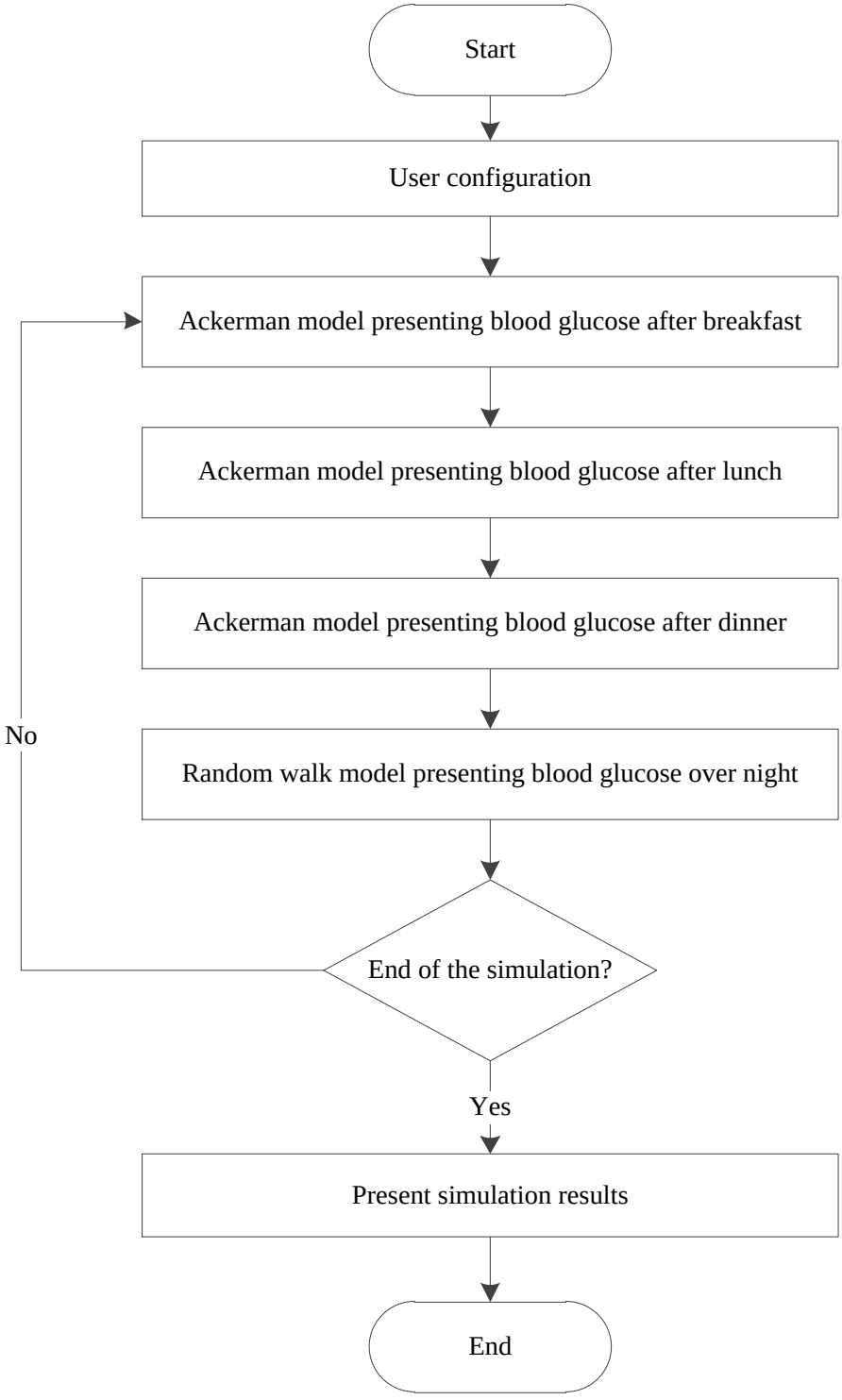
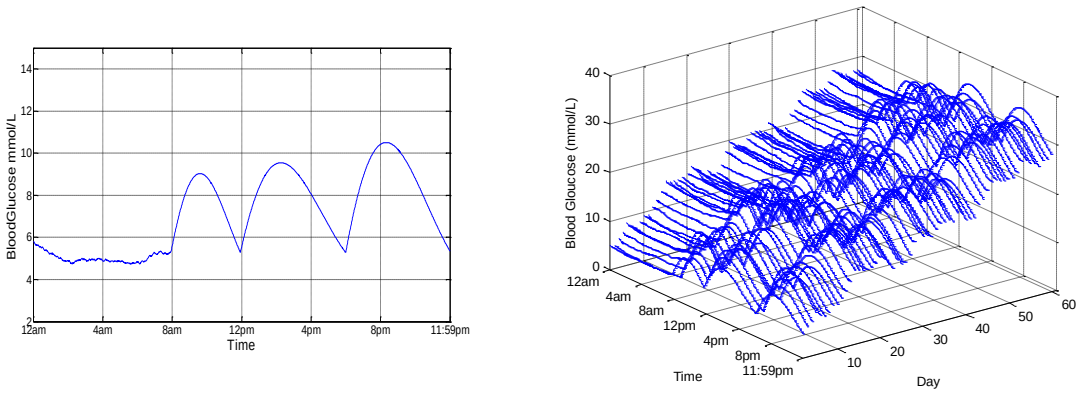


Figure 3-5 Controlled patient agent flowchart

Figure 3-6 (a) shows CPA simulation results in a single day. Again, we see the consistence with results present in the Textbook of Diabetes (Figure 3-4(a)) [58] and actual human blood glucose monitored by CGM (Figure 3-4(b)). This similarity supports the credibility of the simulation. Thus in our model, we integrate the Ackerman model, and the RW model, making this new, enhanced model capable of simulating dynamic BG trajectories. Figure 3-6 (b) shows CPA multi-day simulation results. The vertical axis shows the BG in mmol/L, and the horizontal axis illustrates the time, while the axis into the page shows the date of simulation from the first day to the sixtieth day. Each curve represents daily BG outputs.

However, the actual patient BG trace (see Figure 3-4 (b)) is not as perfectly smooth as that of simulation results (see Figure 3-6 (a)). The actual trace has fluctuations due to the stochastic nature of metabolism as well as sensor errors of CGM technology. The issue of the sensor error is not included in our research, but it might be valuable for future work, since CGM technology continues to face challenges in terms of sensitivity, stability, calibration, and the physiological time lag between blood and interstitial glucose concentration [48, 60]. We currently only incorporate the stochastic nature of metabolism by generating a component of random numbers. Experiments show that it is poorly represented by white noise, so we add a set of RW values within a certain range (from -0.2 to 0.2 mmol/L) on the simulation results. The results are shown in Figure 3-7.



(a) (b)

Figure 3-6 (a) Controlled patient agent single-day simulation results (b) Controlled patient agent multi-day simulation results

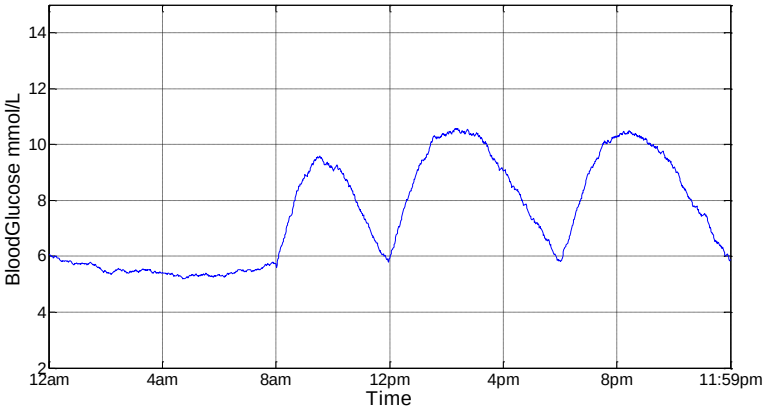


Figure 3-7 CPA single-day simulation results with incorporating stochastic nature of metabolic

3.1.3 Assumptions in the model

We make reasonable assumptions in the design of the CPA as follows:

1. The CPA never misses any of the three meals: breakfast, lunch and dinner.
2. The food schedule of each of these meals is some time from 7am to 9am, from 11am to 1pm, and from 5pm to 7pm respectively.
3. The RW model starts to simulate blood glucose levels 6 hours after the time when dinner is eaten.
4. The CPA never checks up its blood glucose levels.

3.1.4 User interface

As mentioned in the beginning of this chapter, the CPA model incorporates essential attributes of human lifestyle that may affect diabetes, specifically, the amount of food consumed, the food eating schedule and the intensity of exercise and medication. The user interface allows users to manipulate these parameters. Figure 3-8 shows the "General" tab of the user interface of the patient agent in which the parameters of *Instruction from a Physician Agent* and S*imulation Period* can be set. The other parameters are designed for the SPA (see CHAPTER 4). Figure 3-9 shows the "Lifestyle" tab of the user interface.

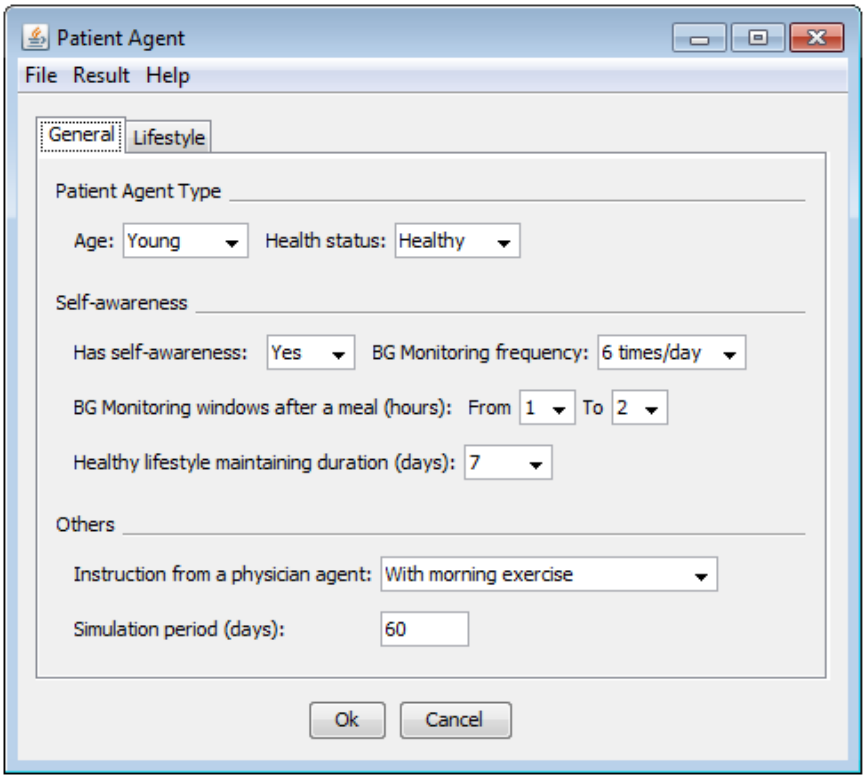


Figure 3-8 User interface of patient agent for general configurations

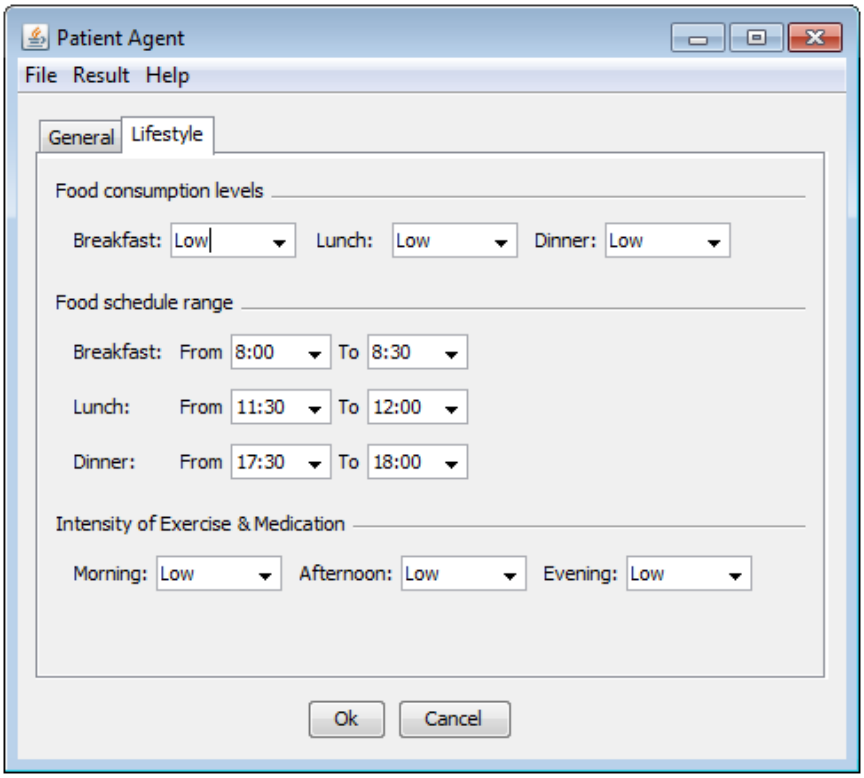


Figure 3-9 User interface of patient agent for lifestyle manipulation

3.2 Experiments and results

To evaluate the CPA model, a number of experiments were conducted in eleven scenarios. In this section, the experiment configurations are discussed firstly. Following that is the recommended BG range for a better understanding of the simulation results, which are presented in the last part.

3.2.1 Experiment configurations

Configurations of the scenarios are shown in Table 3-1. The value of ω for a breakfast was 0.79 and those for a lunch and a dinner were 0.52.

Table 3-1 Eleven scenarios in the experiments

Scenarios	Configuration
Without intervention	The value of F was very high. The value of β was low. Breakfast eating time could be any time from 7:30am to 8:30am. Lunch eating time could be any time from 11:30am to 12:30pm. Dinner eating time could be any time from 17:30pm to 18:30pm.
With morning exercise	The value of β for a breakfast was doubled, and those for a lunch and a dinner were improved by half. Other parameters stayed the same as those in the scenario without intervention.
With afternoon exercise	The value of β for a lunch was doubled, and those for a breakfast and a dinner were improved by half. Other parameters stayed the same as those in the scenario without intervention.
With evening exercise	The value of β for a dinner was doubled, and those for a breakfast and a lunch are improved by half. Other parameters stayed the same as those in the scenario without intervention.
With controlled Breakfast diet	The value of F for a breakfast decreased by 40%. Other parameters stay the same as those in the scenario without intervention.
With controlled Lunch diet	The value of F for a lunch decreased by 40%. Other parameters stayed the same as those in the scenario without intervention.
With controlled Dinner diet	The value of F for a dinner decreased by 40%. Other parameters stayed the same as those in the scenario without intervention.
With controlled breakfast eating time	Breakfast eating time could be any time from 7:45am to 8:15am. Other parameters stayed the same as those in the scenario without intervention.
With controlled lunch eating time	Lunch eating time could be any time from 11:45am to 12:15pm. Other parameters stayed the same as those in the scenario without intervention.
With controlled dinner eating time	Dinner eating time could be any time from 17:45pm to 18:15pm. Other parameters stayed the same as those in the scenario without intervention.
With controlled eating time and diet (all 3 meals)	The value of F for all three meals decreased by 30%. Breakfast eating time could be any time from 7:55am to 8:05am. Lunch eating time could be any time from 11:55am to 12:05pm. Dinner eating time could be any time from 17:55pm to 18:05pm. Other parameters stayed the same as those in the scenario without intervention.

3.2.2 Recommended blood glucose range for diabetic patients

According to the Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada [27], the recommended range of pre-prandial BG should be from 4.0 to 7.0 mmol/L while that of postprandial should be from 5.0 to 10.0 mmol/L. Pre-prandial blood glucose refers to fasting BG, which is a measure of BG before meals. Postprandial BG, by contrast, is a measure of BG after a meal.

3.2.3 Experimental results

The set of observations of BG implemented within the simulation environment includes measures of average BG, average pre-prandial and postprandial BG, times of BG reaching predefined thresholds and CBG.

Table 3-2 Summary blood glucose information of the controlled patient agent

Scenarios	Average BG (mmol/L)	Breakfast Pre/postprandial (mmol/L)	Lunch Pre/postprandial (mmol/L)	Dinner Pre/postprandial (mmol/L)
Without intervention	18.98	16.57/21.42	18.15/22.85	18.23/23.23
With morning exercise	12.09	10.27/13.90	10.33/15.47	10.45/15.50
With afternoon exercise	13.55	11.86/15.96	11.96/16.13	12.04/17.10
With evening exercise	15.00	13.34/17.56	13.34/18.44	13.42/17.62
With controlled breakfast diet	14.58	12.39/15.31	12.17/18.69	12.35/18.96
With controlled lunch diet	12.95	11.05/15.91	10.94/14.75	11.09/17.36
With controlled dinner diet	12.52	10.49/15.34	10.61/16.88	10.69/14.51
With controlled breakfast eating time	12.80	10.39/15.27	10.45/16.77	10.51/16.91
With controlled lunch eating time	12.19	9.85/14.72	9.94/16.23	9.96/16.17
With controlled dinner eating time	12.02	9.64/14.56	9.65/15.97	9.79/16.01
With controlled eating time and diet	9.31	7.62/11.00	7.45/12.01	7.54/12.68

Table 3-3 Times over thresholds of the controlled patient agent

Condition	# of times over 15mmol/L	# of times over 20mmol/L	# of times over 30mmol/L
Without intervention	50	41	13
With morning exercise	31	10	0
With afternoon exercise	40	13	0
With evening exercise	48	25	0
With controlled breakfast diet	40	25	1
With controlled lunch diet	42	17	0
With controlled dinner diet	42	11	0
With controlled breakfast eating time	39	13	0
With controlled lunch eating time	32	8	0
With controlled dinner eating time	35	14	0
With controlled eating time and diet	10	0	0

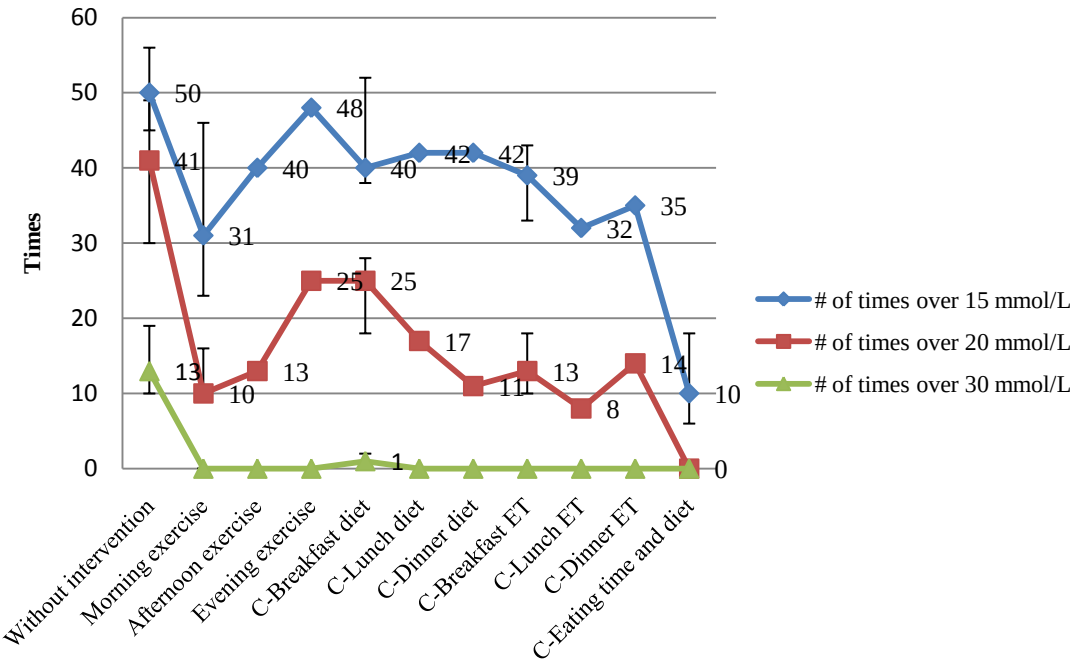
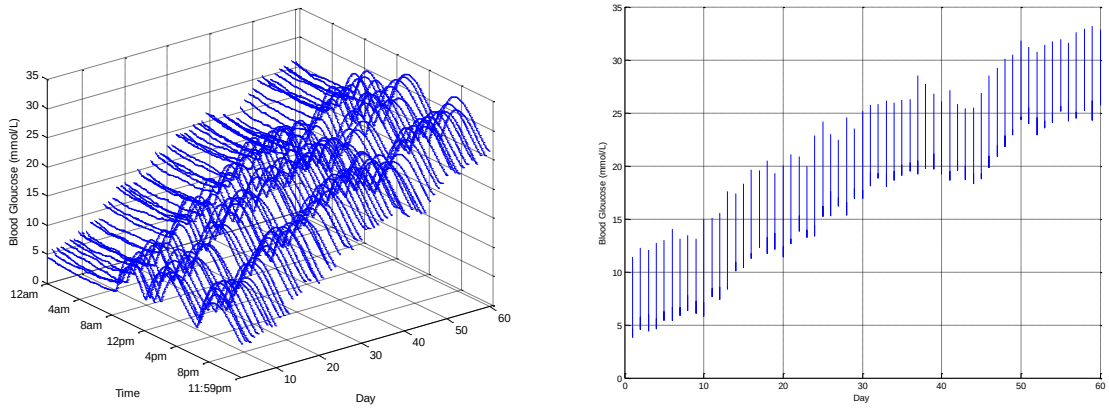


Figure 3-10 Times over thresholds of controlled patient agent

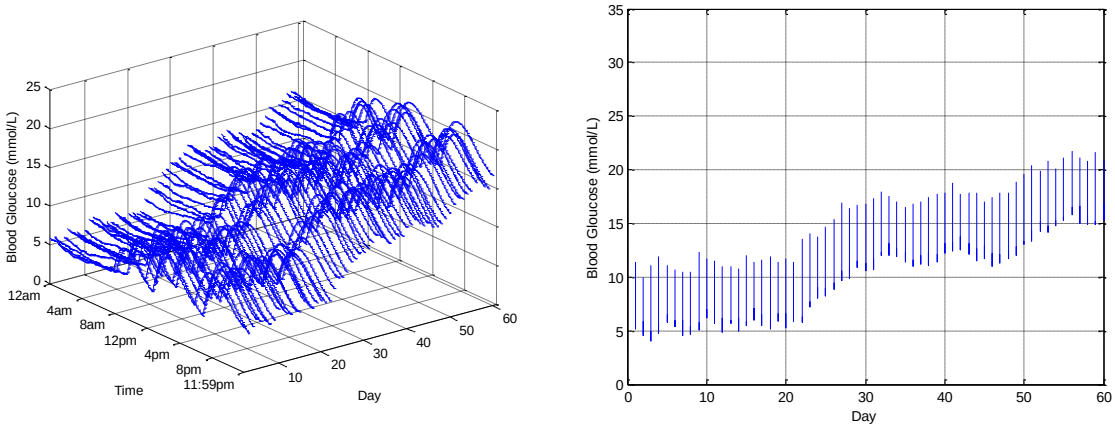
Table 3-2 shows summary BG information which is consistent with former research [61]. Table 3-3 and Figure 3-10 show the number of times the trace surpassed the thresholds (namely 15, 20 and 30 mmol/L) that were predefined as evaluation criteria in the eleven scenarios. The threshold of 30 mmol/L was reached 13 times by the CPA and once in the scenarios *without intervention* and *with controlled breakfast diet*, respectively. The numbers were, by contrast, 0 in the other scenarios. In the scenario *without intervention*, it reached 20 mmol/L 41 times, while it never reached this threshold in the scenario *with controlled eating time and diet*. The number of times it surpassed this threshold varied from 8 to 25 in the other scenarios. As for the threshold of 15 mmol/L, the figures were 50 and 10 in the scenarios *without intervention* and *with controlled eating time and diet* respectively. In the other scenarios, the figures were scattered between 31 and 48. Furthermore, five experiments were conducted for the scenarios *without intervention*, *with controlled morning exercise*, *with controlled breakfast diet*, *with controlled breakfast eating time*, and *with controlled eating time and diet in all meals*, to examine the result variations, which are shown by the error bars in the graph.



(a) (b)

Figure 3-11 (a) Daily blood glucose in 3D format (b) Daily blood glucose range

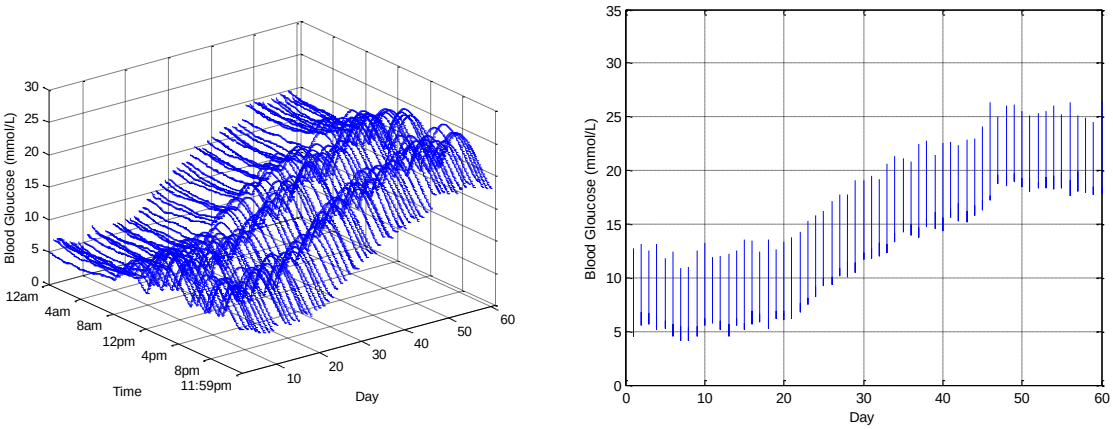
(controlled patient agent in the scenario without intervention)



(a) (b)

Figure 3-12 Daily blood glucose in 3D format (b) Daily blood glucose range

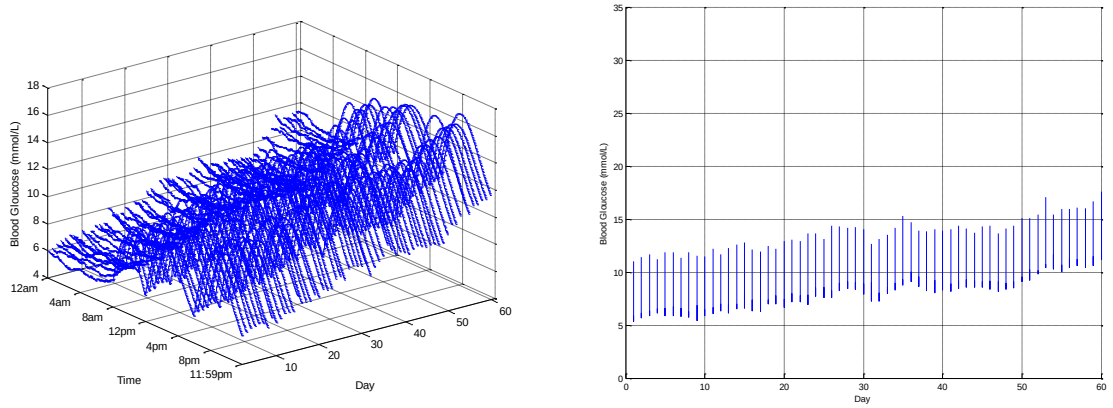
(controlled patient agent in the scenario with morning exercise)



(a) (b)

Figure 3-13 Daily blood glucose in 3D format (b) Daily blood glucose range

(controlled patient agent in the scenario with controlled breakfast diet)



(a) (b)

Figure 3-14: (a) Daily blood glucose in 3D format (b) Daily blood glucose range

(controlled patient agent in the scenario with controlled eating time and diet)

A 3-D graph (see Figure 3-11) shows that the BG levels dramatically increased in the scenario *without intervention*, which is obviously out of control. This is an extreme example that cannot be experimented on a real patient. Figure 3-11 (b) shows the data in a compact format. Figure 3-12 and Figure 3-13 show the BG levels in the scenarios *with morning exercise* and *with controlled breakfast diet* respectively as examples. As can be seen from Figure 3-14, the BG was controlled the best in the scenario *with controlled eating time and diet*. It is noted that the maximum scale of vertical axis in the figures is different. For instance, the scale in Figure 3-11 (a) is 25 mmol/L while that of Figure 3-14 (a) is 18 mmol/L.

3.3 Summary

The CPA model of integrating the enhanced Ackerman model and the RW model in the mobile agent environment has been discussed in this chapter. The Ackerman model is enhanced in two ways: the extension into nights and the incorporation human stochastic behaviour. The third enhancement of addressing human self-awareness is discussed in CHAPTER 4.

This model considers the major influential parameters – food consumption, intensity of exercise and medication, and meal schedule – as the input variables while several BG measures are used as output variables. It also incorporates stochastic human behaviours. The simulation results appear to be consistent with results present in the Textbook of Diabetes (Figure 3-4(a)) [58] and actual human BG monitored by CGM (Figure 3-4(b)), which supports the credibility of the simulation. Thus we determine that the CPA model is capable of simulating dynamic BG trajectories.

A number of experiments are conducted in eleven scenarios of different lifestyles that refer to diabetes treatments recommended by CDA. To augment the efficiency of different lifestyles, an extremely serious case *without intervention* is developed as the base line of these eleven scenarios. The simulation results in this scenario (Figure 3-11) are expected severely high and are consistent with results in a published paper of Paranjape et al [61]. The simulation results in the eleven scenarios demonstrate how the patient's lifestyle can influence the control of blood glucose levels by counting the times the results fell out of the target range.

The major observations from these experiments illustrate that the model is capable of adequately representing diabetic patients and of evaluating their dynamic behaviours. This model can help patients explore their prognosis if they are not meticulous in controlling their blood glucose levels.

CHAPTER 4

SELF-AWARE PATIENT AGENT MODEL

The CPA incorporates major influential parameters in diabetes management and it can represent typical diabetic patients. However, human behaviour is far more complicated than the proposed factors. For instance, people may frequently sample their BG and respond to knowledge of their own condition, which is called SMBG and self-management. To incorporate such issues, the SPA is constructed as an enhancement of the CPA. This model also incorporates risk factors of age and health status.

This chapter begins with a discussion of SMBG and then provides the architecture and algorithm of the SPA model. Following that are simulation experiments and results. A summary is presented in the last part.

4.1 Self monitoring blood glucose

SMBG is one of the major components of diabetes management. An exhaustive review of SMBG is beyond the scope of this thesis; nonetheless we provide a brief introduction for a better understanding of the term “self-awareness”.

The effectiveness of SMBG has been demonstrated in Type 1 diabetes and insulin-dependent Type 2 diabetes with the aim of optimized control of blood glucose [62, 63]. However, SMBG remains debatable in non-insulin treated patients with Type 2 diabetes [64]. Some researchers argue that SMBG for non-insulin treated patients with Type 2 diabetes may lead to improved glycemic control [15, 16]. This is because, theoretically, SMBG by patients with Type 2 diabetes could result in better compliance with diet and exercise advice and with medication regimens, eventually resulting in better

glycemic regulation [14]. This hypothesis of improvement is based on the fact that self-management or lifestyle changes are facilitated by SMBG. Some other researchers have contrasting opinions, believing it is a waste of money [65]. Nonetheless, SMBG for people with Type 2 diabetes may lead to improved glycemic control and is commonly recommended [15, 16]. According to the recommendations of the ADA [66], SMBG should be utilized as follows.

- To achieve the optimal postprandial glycemic target
- In patients on intensive insulin therapy (at least 3 times per day)
- In patients on non-intensive insulin therapy or not using oral hypoglycemic agents or treated with diet therapy alone, to achieve the optimal glycemic target

4.2 Method

4.2.1 Self-aware patient agent model architecture

Figure 4-1 shows the SPA architecture. Based on the architecture of the CPA, it incorporates a sensor *in silico* for sampling as well as a reasoning model of behaviour adjustment. This is analogous to human patients pricking their finger and using a drop of blood to measure their own BG. It seems reasonable to expect that values which are out of the desired bounds would result in the human subject altering to some extent his/her own behaviour in terms of food intake, exercise, adherence to medications, etc [1]. The method of generating BG in the SPA model is the same as those in the CPA model. The SPA also assimilates risk factors of age and health status, which is discussed in CHAPTER 5 in detail.

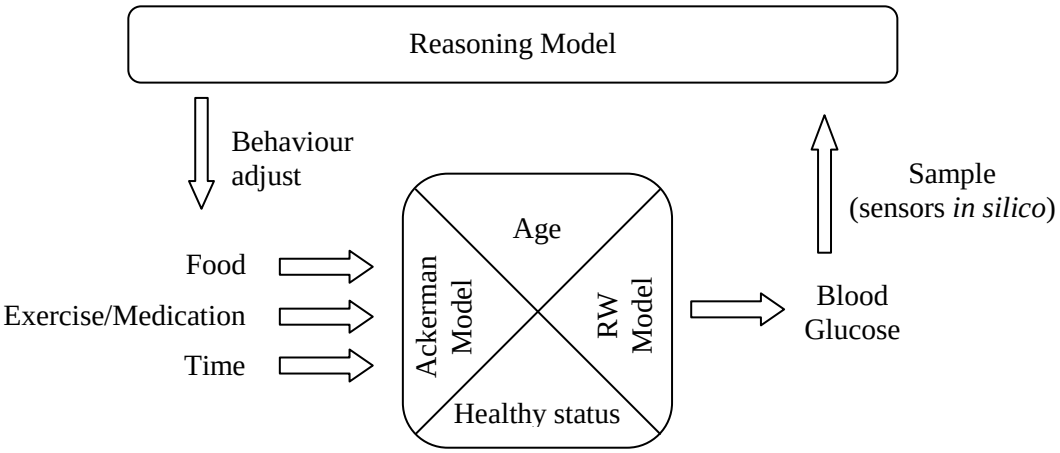


Figure 4-1 Self-aware patient agent architecture

4.2.2 Self-awareness

The concept of self-awareness derives from SMBG and self-management in diabetes treatment. Relating issues are introduced into the SPA as four factors: monitoring frequency (MF), time of monitoring, rules of behaviour change, and duration of behaviour maintaining. Behaviour change refers to adopting a healthier lifestyle.

Time windows instead of a specific time are defined to monitor the BG level. The SPA randomly picks a time within the windows to check its BG, which is representative of stochastic human behaviour. If the SPA gets two consecutive bad measures, it will adopt a healthier lifestyle and maintain it for a specific period of seven days or one month. A detailed design of MF is presented in section 5.2.1.

4.2.3 Self-aware patient agent algorithm

Figure 4-2 shows the SPA flowchart. The system first receives configurations from users. If the setting of *Has Self-Awareness* is *No,* the patient agent will be a CPA. The algorithm of the CPA is discussed in section 3.1.2. If it is *Yes*, the SPA model will run till the end of the simulation. During the simulation, the sensor *in silico* samples the BG level within a monitoring time window and in a frequency according to users' setting. At the end of each day, the system checks whether the rule of behaviour change is satisfied or not. If it is, the SPA will adopt a healthier lifestyle. The details of a healthier lifestyle are discussed in section 4.3.1. If it is not, the SPA will check whether it is maintaining healthier behaviour and whether it is at the end of its healthier behaviour maintenance. If both of them are *Yes*, the SPA restores original user configurations on the lifestyle. Otherwise, the model will continue adopting this current lifestyle or behaviour. At the end of the simulation, the results will be presented.

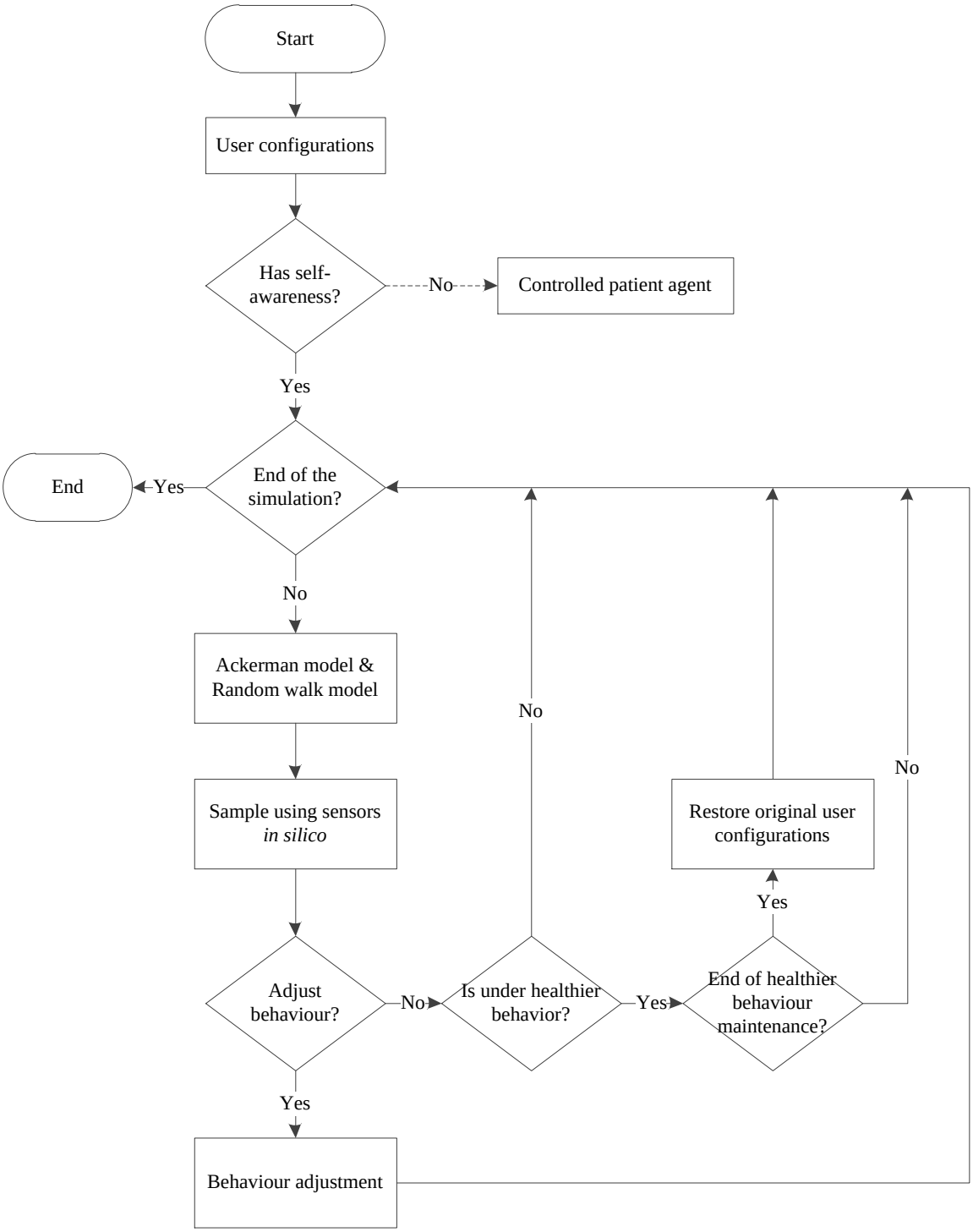


Figure 4-2 Self-aware patient agent flowchart

4.2.4 User interface

Through the "General" tab of the user interface (see Figure 3-8), users can configure P*atient Agent Type* including age and health status and the self-awareness parameters. The parameters of *Instruction from a Physician Agent* and *Simulation Period* can also be set in this tab. The settings of lifestyle including A*mount of Food Consumption*, *Food Eating Schedule* and *Intensity of Exercise and Medication* can be manipulated in the "Lifestyle" tab of the user interface (see Figure 3-9). It should be noted that these configurations of lifestyle may be changed later by the reasoning model of the SPA.

4.3 Experiments and results

In order to evaluate the SPA model and compare it with the CPA model, a number of experiments were conducted in the same scenarios as those of the CPA model (see section 3.2.1).

In this section, experiment configurations and results are provided.

4.3.1 Experiment configurations

The parameters of F, β, t, and ω in the SPA model were set up the same as that of the CPA model (provided in section 3.2.1). Table 4-1 shows the configuration of self-awareness for the experiments. Table 4-2 illustrates the method of reflecting healthier lifestyle or behaviour change to parameters of the Ackerman model. For instance, if adopting a *morning healthier lifestyle*, the value of F of the Ackerman model representing breakfast decreased by 30% while the value of β increased by 30%. The

time allotted to eating breakfast had a more restraining window, from 7:45am to 8:15am. These alternations would lead to better BG control.

Table 4-1 Configurations of self-awareness of the self-aware patient agent

Factors	Configurations
Monitoring frequency	3 times per day: monitoring postprandial blood glucose of each meal
Time windows of self monitoring	Before a meal: from 0 to 20 minutes After a meal: from 2 to 3 hours
Rules of adopting a healthier lifestyle	Getting two consecutive bad measurements
Duration of maintaining the healthier lifestyle	7 days

Table 4-2 Coefficients of parameter adjustment in the Ackerman model

Type	Configuration
Morning healthier lifestyle	The value of F for a breakfast decreased by 30%. The value of β for a breakfast increased by 30%. Breakfast eating time could be any time from 7:45am to 8:15am.
Afternoon healthier lifestyle	The value of F for a breakfast decreased by 30%. The value of β for a breakfast increased by 30%. Lunch eating time could be any time from 11:45am to 12:15pm.
Evening healthier lifestyle	The value of F for a breakfast decreased by 30%. The value of β for a breakfast increased by 30%. Dinner eating time could be any time from 17:45pm to 18:15pm.

4.3.2 Experimental results

Measures of average BG, average pre-prandial and postprandial BG, times of BG reaching predefined thresholds and CBG were observed. Table 4-3 shows summary BG information including average BG and average pre/postprandial BG of the meals.

Table 4-3 Summary blood glucose information of self-aware patient agent

Condition	Average BG (mmol/L)	Breakfast Pre/postprandial (mmol/L)	Lunch Pre/postprandial (mmol/L)	Dinner Pre/postprandial (mmol/L)
Without intervention	12.47	10.71/14.56	10.73/15.57	10.81/15.60
With morning exercise	10.07	8.63/11.87	8.58/12.82	8.71/12.93
With afternoon exercise	10.61	9.42/12.63	9.38/12.61	9.51/13.25
With evening exercise	7.76	6.07/10.20	6.13/11.15	6.21/10.40
With controlled breakfast diet	12.23	10.89/13.07	10.92/14.96	10.98/14.97
With controlled lunch diet	10.01	8.51/12.36	8.50/11.98	8.57/13.12
With controlled dinner diet	11.68	10.35/13.83	10.43/14.67	10.51/13.13
With controlled breakfast eating time	12.13	10.56/14.03	10.50/14.78	10.66/15.00
With controlled lunch eating time	12.86	11.33/14.87	11.34/15.60	11.41/15.64
With controlled dinner eating time	11.51	9.80/13.54	9.87/14.37	9.95/14.61
With controlled eating time and diet	6.99	5.30/8.69	5.29/9.66	5.31/10.33

Table 4-4 Times over thresholds of the self-aware patient agent

Condition	# of times over 15mmol/L	# of times over 20mmol/L	# of times over 30mmol/L
Without intervention	38	12	0
With morning exercise	14	0	0
With afternoon exercise	16	0	0
With evening exercise	3	0	0
With controlled breakfast diet	28	0	0
With controlled lunch diet	11	0	0
With controlled dinner diet	23	0	0
With controlled breakfast eating time	34	0	0
With controlled lunch eating time	42	0	0
With controlled dinner eating time	31	0	0
With controlled eating time and diet	0	0	0

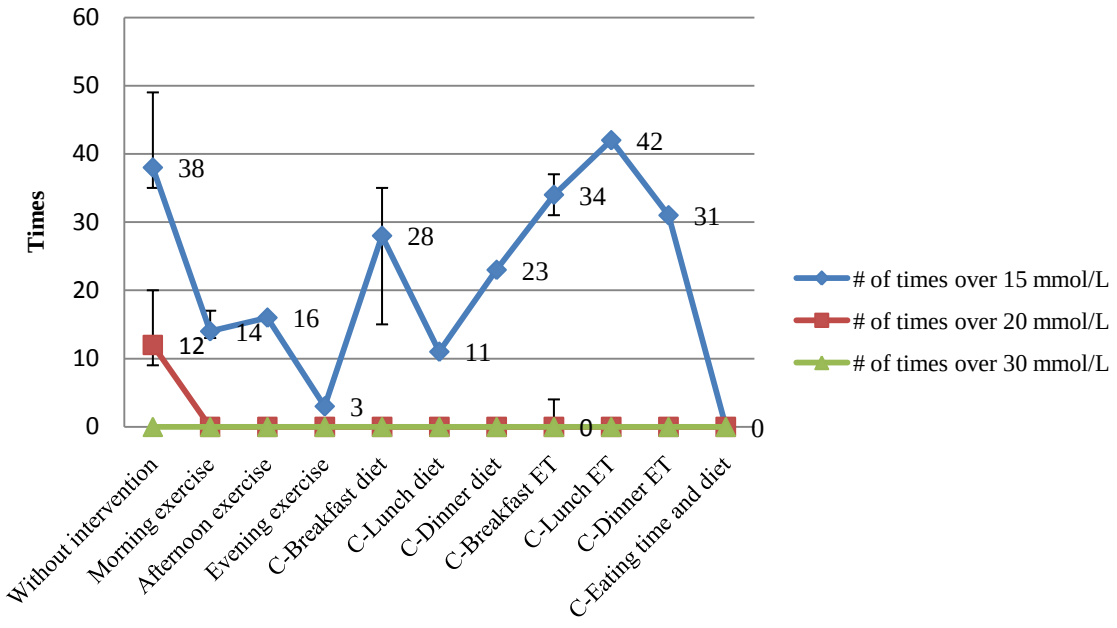
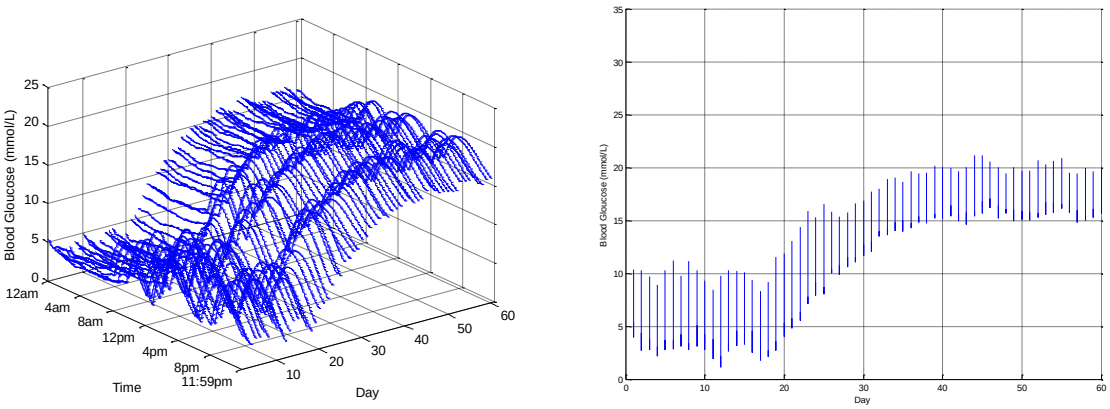


Figure 4-3 Times over thresholds of the self-aware patient agent

According to the simulation results (see Table 4-4 and Figure 4-3), the SPA never hit 30 mmol/L in the two-month simulation. It only reached 20 mmol/L 12 times in the scenario *without intervention*. In contrast, it hit 15 mmol/L 38 times in the scenario *without intervention* while it never hit this threshold in the scenario *with controlled eating time and diet*. Also, the error bars show the variation of five experiments in the scenarios *without intervention*, *with controlled morning exercise*, *with controlled breakfast diet*, *with controlled breakfast eating time*, and *with controlled eating time and diet in all meals*.

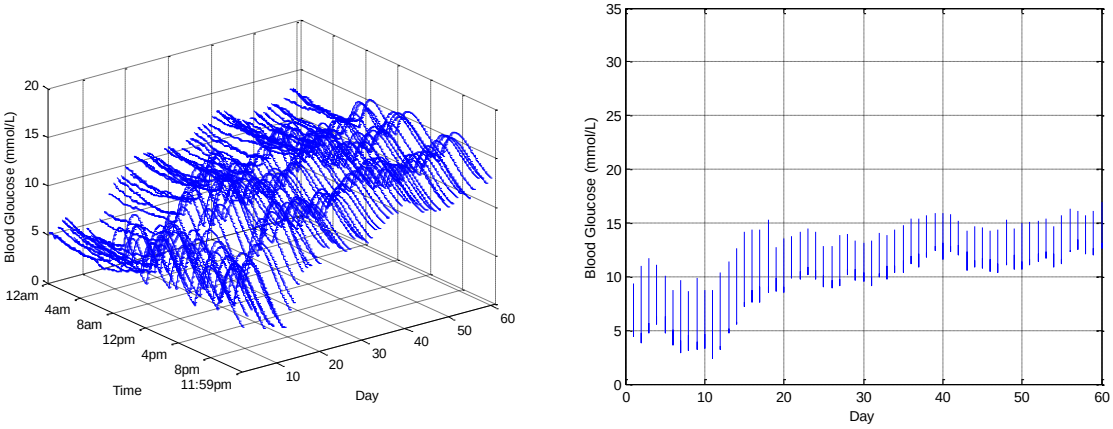
As can be seen from Figure 4-4, the SPA model had better-controlled BG levels compared to the CPA model, although BG levels steadily increased from the twentieth day to the fortieth day in the scenario *without intervention*. Figure 4-5 and Figure 4-6 show the CBG levels in the scenario *with morning exercise* and *with controlled breakfast diet*, respectively. Figure 4-7 shows the CBG levels in the scenario *with controlled eating time and diet*, in which we can see the BG level was controlled within target levels most of time in this scenario.



(a) (b)

Figure 4-4 (a) Daily blood glucose in 3D format (b) Daily blood glucose range

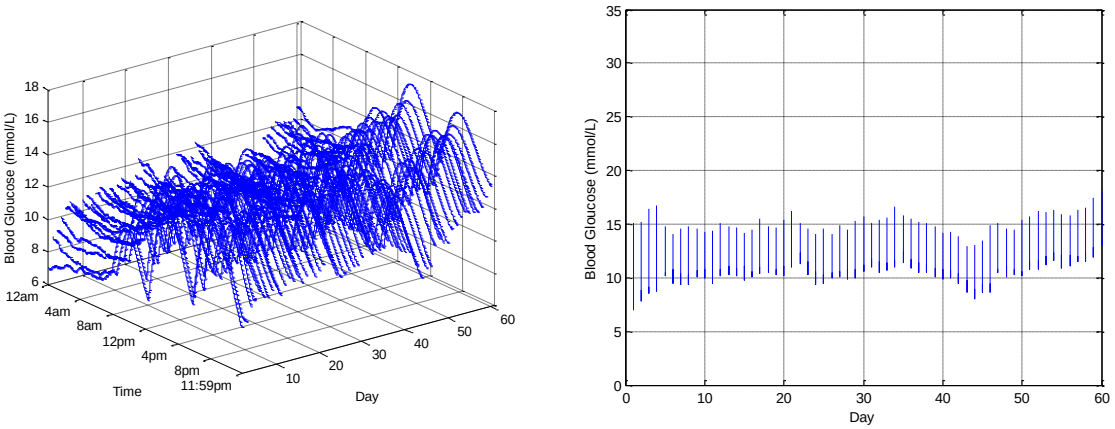
(self-aware patient agent in the scenario without intervention)



(a) (b)

Figure 4-5 Daily blood glucose in 3D format (b) Daily blood glucose range

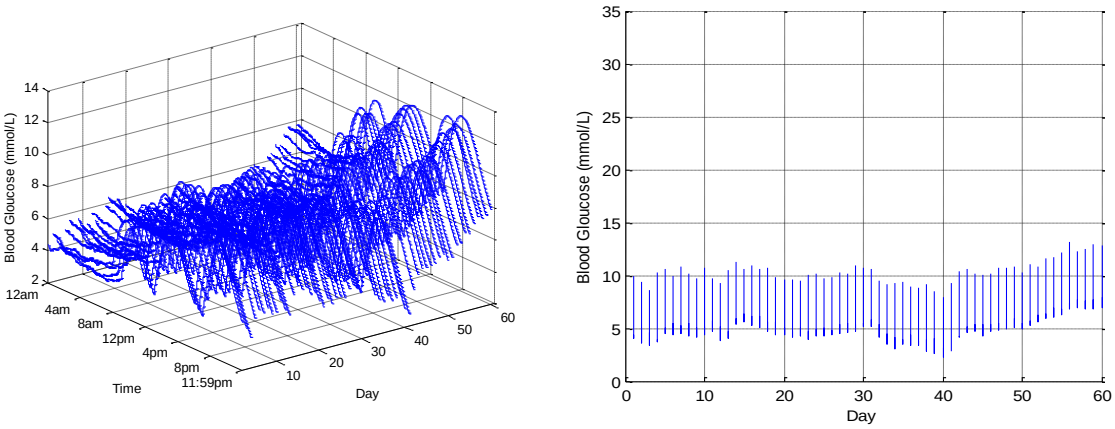
(self-aware patient agent in the scenario with morning exercise)



(a) (b)

Figure 4-6 Daily blood glucose in 3D format (b) Daily blood glucose range

(self-aware patient agent in the scenario with controlled breakfast diet)



(a) (b)

Figure 4-7 (a) Daily blood glucose in 3D format (b) Daily blood glucose range

(self-aware patient agent in the scenario with controlled eating time and diet)

Figure 4-8 shows the comparison of the CPA and the SPA in the range of numbers over 15 mmol/L. The SPA model had better performance in terms of controlling BG levels in most scenarios except the scenario of *with controlled lunch eating time*. The best situation, which the threshold was never reached, occurred in the scenario *with controlled eating time and diet* of the SPA model.

It should be noted that the results shown in Figure 4-8 are an example of a sixty-day simulation experiment. Since the patient agent model captures stochastic characters of people, the observations may change in a range and the CPA may perform better than the SPA occasionally.

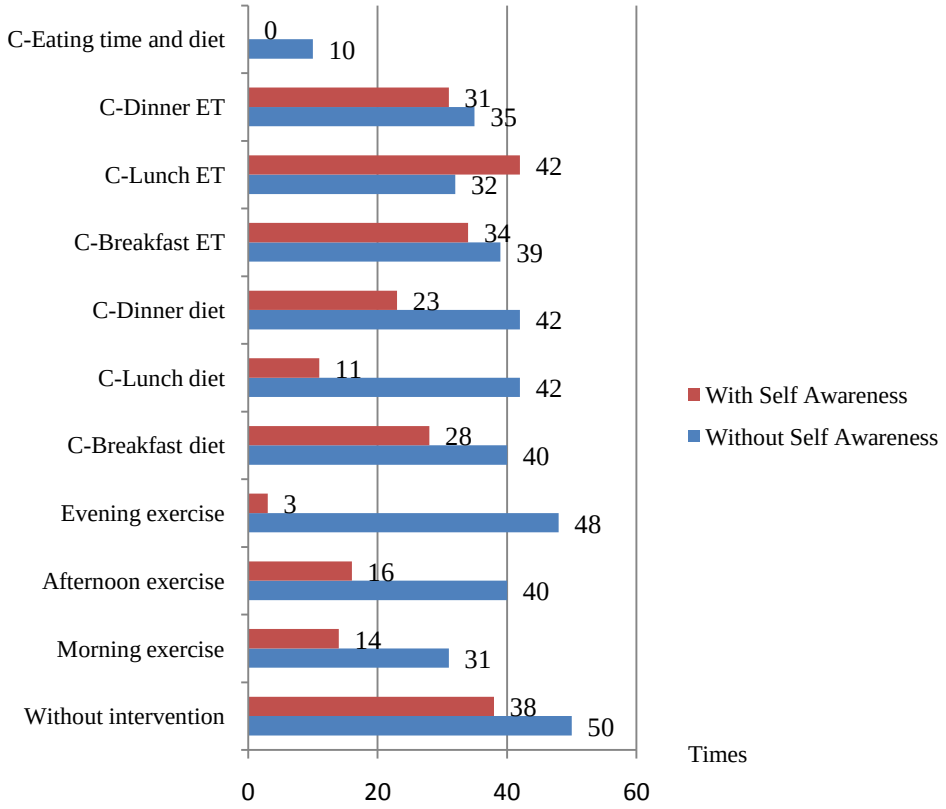


Figure 4-8 Results comparison in times of over 15 mmol/L

4.4 Summary

The SPA is an enhancement of the CPA, in which the Ackerman model is improved by incorporating self-awareness. Besides major influential parameters of influencing diabetes considered by the CPA, the SPA further integrates sensors *in silico* and a reasoning model of changing behaviours, which is analogous to the human patient pricking his/her finger and using a drop of blood to measure his/her own BG.

Experimental results showed the capability of the SPA in demonstrating the effectiveness of adopting a healthier lifestyle and self-awareness in a quantitative way. Due to the self-awareness, the SPA controlled the BG levels better than the CPA in all scenarios except the scenarios *with controlled lunch eating time*. These results showed the importance of SMBG and self-management of lifestyle in response to the samples.

Risk factors of age and health status are integrated into the SPA model by incorporating coefficients into F, β, and ω. This is discussed in more detail in the next chapter. Additionally, only the MF of *3 times per day* is considered in this chapter; and the other levels of MF are presented in the next chapter.

CHAPTER 5

BLOOD GLUCOSE MONITORING FREQUENCY EVALUATION

As mentioned in section 4.1, SMBG for people with Type 2 diabetes is commonly recommended and the efficacy of SMBG has been demonstrated in the SPA model. The hypothesis is based on the fact that self-management or lifestyle changes are facilitated by SMBG. The other hypothesis is that the samples can properly represent the CBG, and obviously, the more samples taken, the better presentation. However, the frequency of monitoring is an issue due to the related cost, discomfort and potential infection. People expect an optimal frequency of SMBG instead of either too much or too little.

In this chapter, signal analysis techniques are utilized to evaluate blood glucose monitoring frequency in the SPA model. We first briefly examine the history of the use of these techniques in the study of diabetes physiology. Following this, we propose the details of the method, experiments and simulation results. The chapter is summarized in the last section.

5.1 Signal analysis techniques in diabetes physiology

The use of Spectral/Correlation analysis in the study of diabetes physiology started in the early 1990s. This method can easily quantify the dynamic relationship between paired time series, e.g., glucose and insulin [67-70]. The maximum cross-correlation between glucose and insulin values, for instance, are found to indicate where they are nearly in phase[67].

5.2 Evaluation method

In this work, we propose signal processing techniques of calculating Normalized Cross-Correlation at Zero Lag (NCCZL) and Average Value Deviation (AVD) between CBG and interpolation of samples generated by the SPA to examine the effectiveness of different levels of MF. Through observing mean and variance of NCCZLs and AVDs, an optimal MF can be acquired for a specific SPA. An example of the CBG, the interpolation, and the samples can be seen in Figure 5-2 (a) in which the blue solid line represents the CBG; the red dashed line represents the interpolation; and the red circles represent the samples.

In this section, we first define MFs and then discuss the interpolation, the NCCZL and the AVD in turn. Following that, the category of the SPA is presented to map the population of diabetes. Experiments, simulation results and a summary are also given.

5.2.1 Blood glucose monitoring frequency

As mentioned in section 3.2.2, BG is classified as pre-prandial and postprandial BG, which refers to BG before and after a meal, respectively. We also assume that the SPA never misses a major meal. Therefore, there are six critical times of BG in the model, namely, BG before and after a breakfast, before and after a lunch, and before and after a dinner.

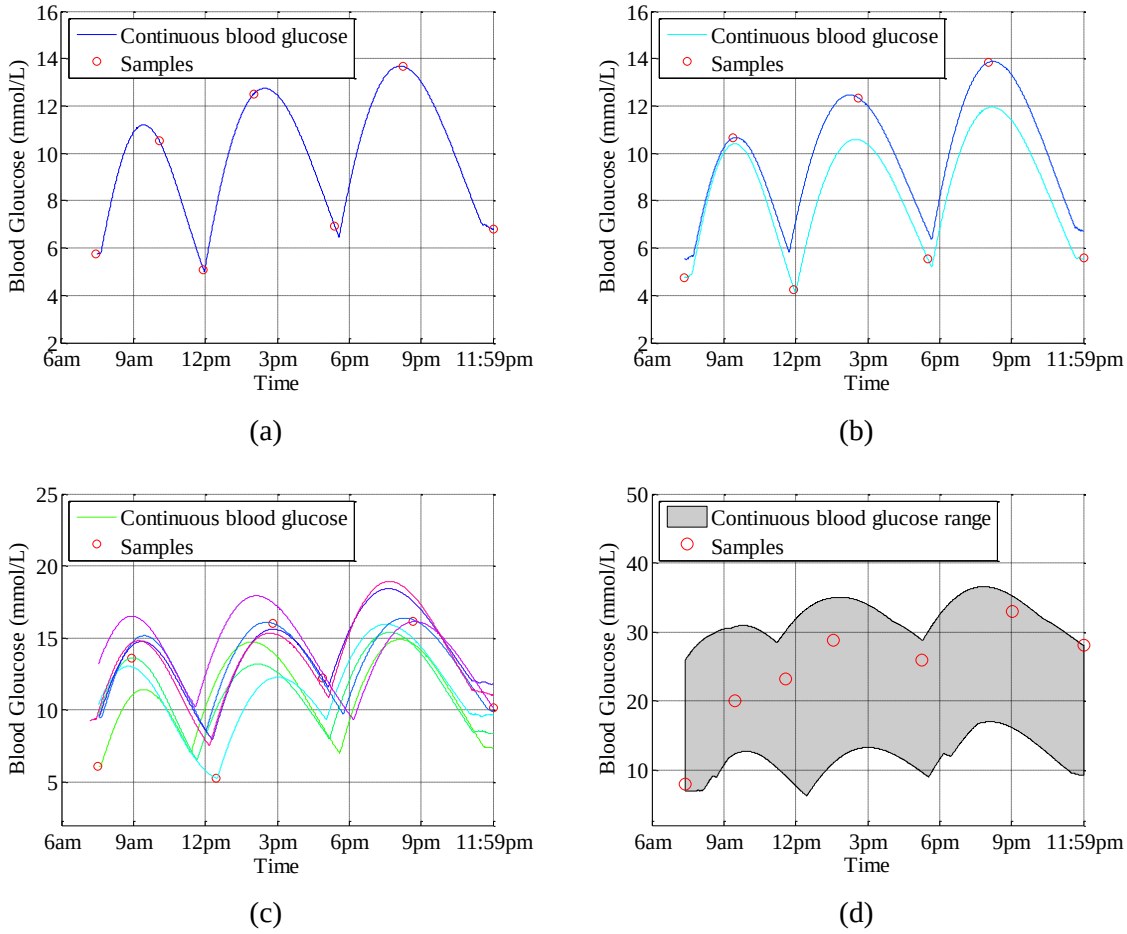


Figure 5-1 Samples with monitoring frequency of

(a) 6 times/day (b) 3 times/day (c) 1 time/day (d) 1 time/week

In this work, we consider four options of MF: *6 times per day*, *3 times per day*, *1 time per day* and *1 time per week*. Figure 5-1 shows sampling protocols of the SPA. The rationale is trying to cover the BG at the six critical points as soon as possible. Under the MF of 6 times per day, the SPA can get all six critical points in a single day (see Figure 5-1 (a)). To form a sinusoid-like curve of interpolation, an extra sample (shown by the last red circle) is performed by the system, which is the pre-prandial BG of breakfast of the next day. This also applies to the other MFs. For the option of *3 times per day*, the SPA checks pre-prandial and postprandial BG of the three meals in a cyclical way, e.g., it monitors the pre-prandial BG for three meals in the first day, while it monitors the postprandial ones in the second day. This is shown in Figure 5-1 (b) in which the green line represents the first day's CBG and the blue represents the second day's CBG. As can be seen in Figure 5-1 (c) and (d), the BG is also cyclically monitored in the options of *1 time per day* and *1 time per week*. More exactly, the SPA monitors BG at the critical points in a specific order: the pre-prandial BG of breakfast, the postprandial BG of breakfast, the pre-prandial BG of lunch, the postprandial BG of lunch, the pre-prandial BG of dinner, and the postprandial BG of dinner. Once the BG at critical times is monitored, the samples can be interpolated to express a daily pattern (see red dashed lines in Figure 5-2). The interpolation will be discussed in the section 5.2.1.

5.2.2 Self-aware patient agent categories

In the real world, obviously, the frequency for SMBG can vary according to the individual patient. To map the diversity of Type 2 diabetic patients, the SPA is categorized into nine types in terms of health status and age levels: Healthy & Young, Healthy & Middle-aged, Healthy & Elderly, Medium & Young, Medium & Middle-aged, Medium & Elderly, Sick & Young, Sick & Middle-aged, and Sick & Elderly. With different parameter settings of the Ackerman model, each type of SPA is capable of representing a group of human patients.

The parameters of the Ackerman model are gained coefficients to reflect the different response of input information for the nine types of SPA. The foundation of the coefficients is from Jansson's study. They utilize the Ackerman model to analyze the BG curves obtained during the oral glucose tolerance test in 378 cases and illustrate that the parameters of ω, F, and β are linear functions of ages [71]. Based on this, we define a class of linear functions to calculate the parameter of ω, and gains for F and β to mimic individual physical response of the same amount of food consumption, and the similar intensity of exercise and medication.

$$\omega_j = -0.03 \times H_k - 0.03 \times A_i + 0.52 \tag{3.1}$$

$$G_{fj} = 0.03 \times H_k + 0.06 \times A_i + 1 \tag{3.2}$$

$$G_{\beta j} = -0.03 \times H_k - 0.06 \times A_i + 1 \tag{3.3}$$

where ω_j (j = 1, 2, …, 9) is the system frequency for a type of SPA with j;G_{fj} is the gain of F; $G_{\beta j}{}_j$ is the gain of β; k is the age level with 1 representing Young, 2 representing Middle-aged, and 3 representing Elderly; i is the health status with 1 representing

Healthy, 2 representing Medium, and 3 representing Sick. The values of H_k are 0, 1 or 2 with k. Similarly, the values of A_i are 0, 1 or 2 with i. Hence, each SPA has a specific ω, and coefficient for F and β. For example, for the Healthy & Young Patient agent, the ω is $\omega_1(0.52)$, F, and β are supposed to multiply G_{f1} (1) and $G_{\beta 1}$ (1) respectively.

5.2.3 Interpolation of samples

In this subsection, the two methods of linear and high order interpolation are discussed. After comparing them, the linear method is adopted in this work.

5.2.3.1 Linear interpolation

Linear interpolation is generally straight-forward. However, it should be noted that the amount of data points that are interpolated into a pair of samples should be the same as the number of time series between the two samples in order to calculate the NCCZL between CBG and interpolation. For instance, if the first sample is monitored at 7am and the second sample is monitored at 1pm, 360 data points will be interpolated between the two sample points because the patient agent model generates a level of BG each minute. In other words, the patient agent generates 360 BG points between 7am and 1pm. Since the CBG is a function of time series, the CBG and the interpolation have the same amount of data points, allowing them to be easily compared and cross-correlated.

If the SPA monitors its BG *6 times per day*, it can have 6 samples everyday, which, plus the extra sample, represents the daily trajectory of the CBG. As for the MFs of *3 times per day*, *1 time per day* and *1 time per week*, the SPA is able to have enough samples of analogue the CBG in two, six, and forty-two days respectively. Figure 5-2 and

Figure 5-3 shows the linear interpolation results in the four types of MF of Healthy & Young and Sick & Elderly SPA models, respectively.

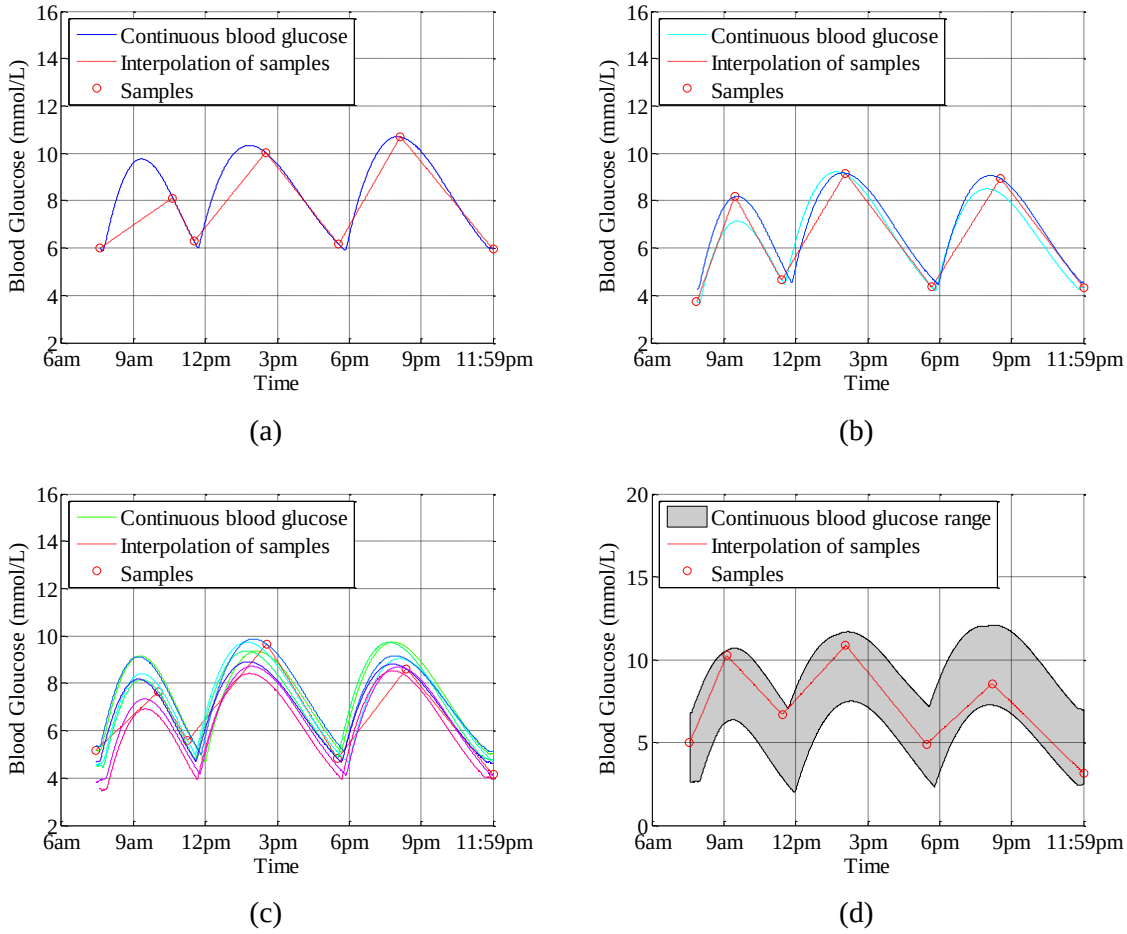


Figure 5-2 The Healthy & Young SPA's continuous blood glucose, linear interpolation and samples with monitoring frequency of (a) 6 times/day (b) 3 times/day (c) 1 time/day (d) 1 time/week

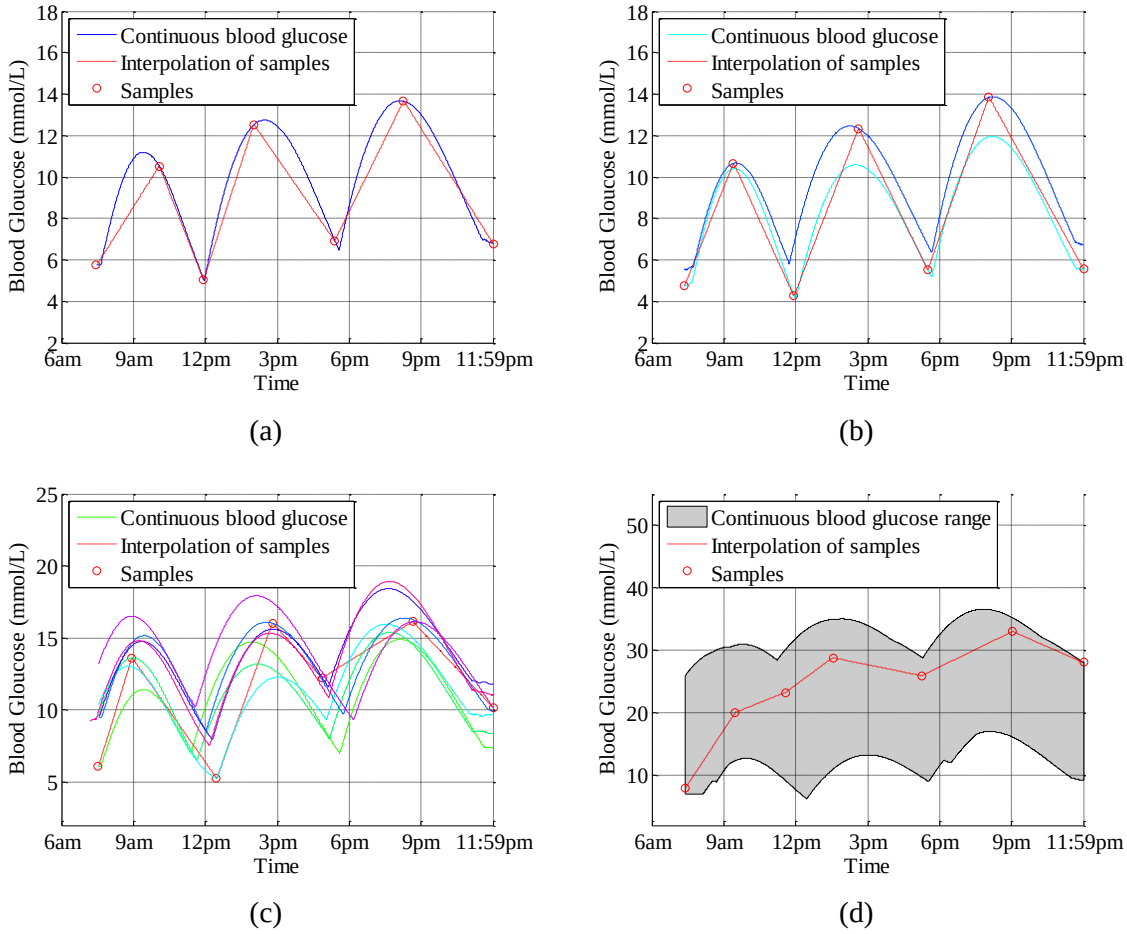


Figure 5-3 The Sick & Elderly SPA's continuous blood glucose, linear interpolation and samples with monitoring frequency of (a) 6 times/day (b) 3 times/day (c) 1 time/day (d) 1 time/week

5.2.3.2 Higher order polynomial interpolation

For the method of higher order polynomial interpolation, Piecewise Cubic Hermite Interpolating Polynomial (PCHIP) in MATLAB is used to interpolate the samples.

Figure 5-4 (a) shows an example of PCHIP of the Healthy & Young SPA within the MF of 6 times per day. The detail of samples and monitoring time in this example is shown in Table 5-1. The piecewise polynomial generated by PCHIP in this case is $P(t) = c_1 t^3 + c_2 t^2 + c_3 t + c_4$. It generates six polynomials to fit the seven samples where coefficients are shown in Table 5-2. Figure 5-5 shows the high order interpolation of PCHIP in the four types of MF for the Sick & Elderly SPA model.

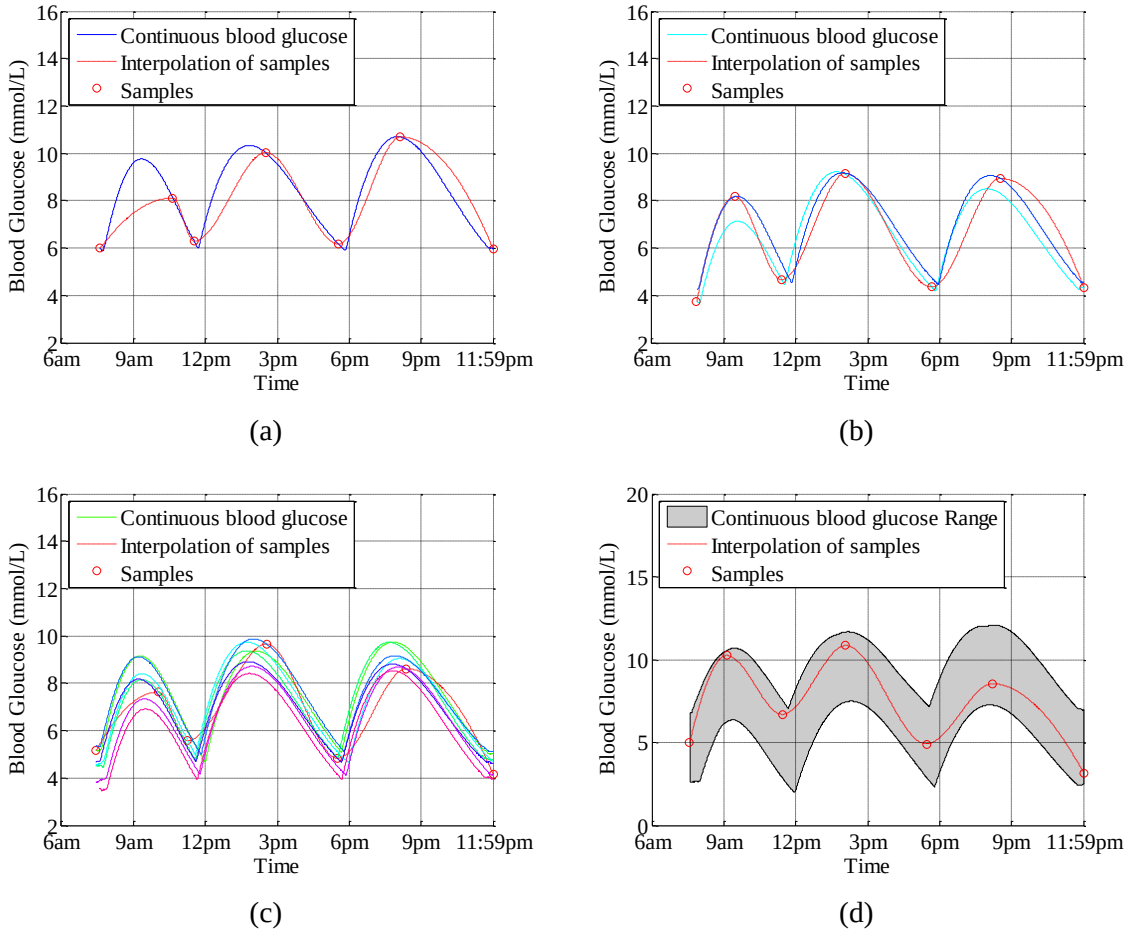


Figure 5-4 The Healthy & Young SPA's continuous blood glucose, high order polynomial interpolation and samples with monitoring frequency of (a) 6 times/day (b) 3 times/day (c) 1 time/day (d) 1 time/week

Table 5-1Samples and monitoring time in a simulation example

# of sample	1	2	3	4	5	6	7
BG (mmol/L)	5.99	8.11	6.29	10.03	6.17	10.69	5.95
Monitoring time	07:36am	10:38am	11:31am	2:31pm	5:33pm	8:08pm	12:00am

Table 5-2 Piecewise cubic Hermite interpolating polynomial coefficients

# of sample	c_1	c_2	c_3	c_4
1	-0.15	-1.82	4.09	5.99
2	3.64	-5.46	0	8.11
3	-7.48	11.22	0	6.29
4	7.72	-11.58	0	10.03
5	-9.04	13.56	0	6.17
6	0.11	-4.85	0	10.69

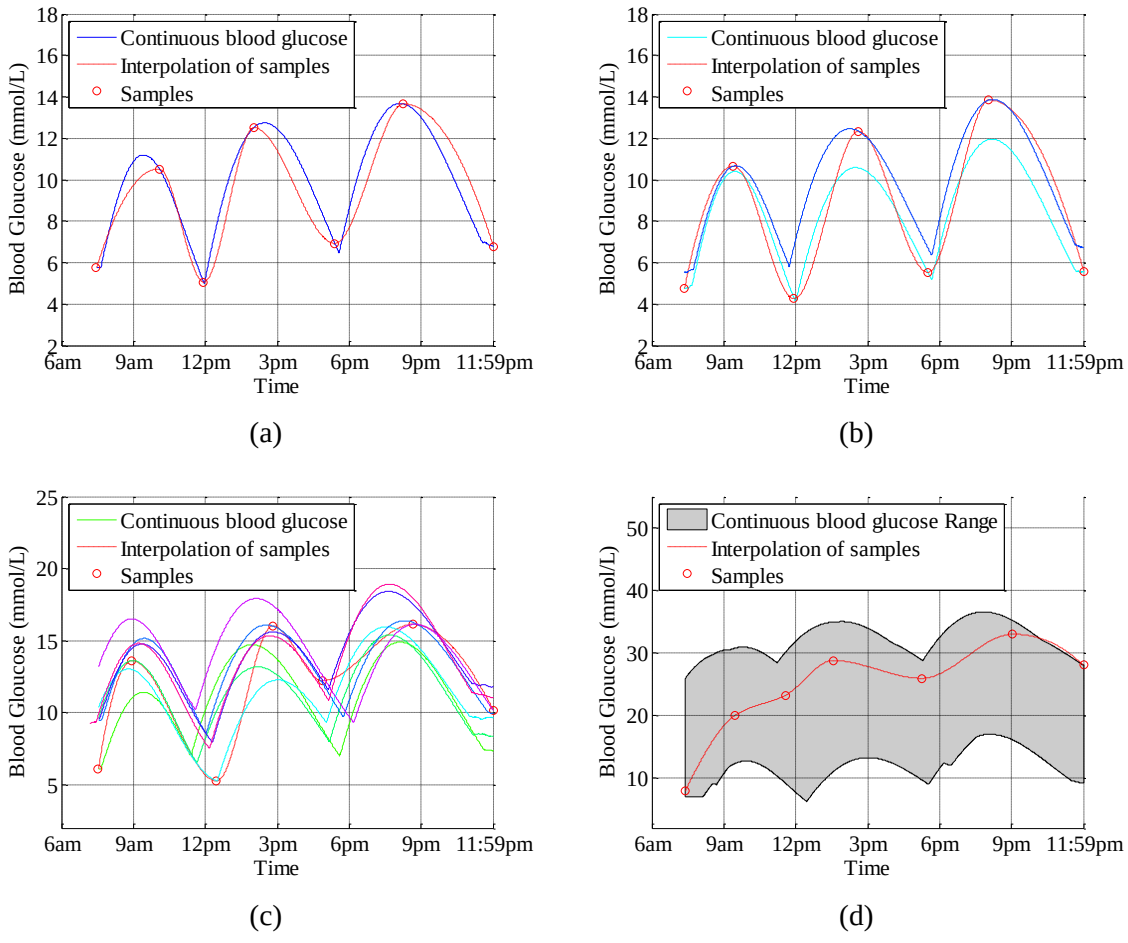


Figure 5-5 The Sick & Elderly SPA's continuous blood glucose, high order polynomial interpolation and samples with monitoring frequency of (a) 6 times/day (b) 3 times/day (c) 1 time/day (d) 1 time/week

5.2.3.3 Comparison of linear and high order polynomial interpolation

In terms of the observations of the NCCZLs, the difference between the two methods is insignificant. The method for calculating NCCZLs is discussed in the next section. As can be seen from Table 5-3, the greatest difference is 0.05 occurring in the MF of *6 times per day* and *1 time per week* of the Healthy & Young SPA model. The results of the Sick & Elderly SPA model are even more insignificant (see Table 5-4). Therefore, it is of little benefit to invest great effort and calculation cost into using high order polynomial interpolation. In addition, high order polynomial interpolation may cause confusion, as it tends to only draw straight lines between samples rather than sinusoid-like curves. Therefore, we use linear interpolation in this work.

Table 5-3 Comparison between linear and high order polynomial interpolation in the Healthy & Young SPA model

Healthy & Young	6 Times/Day	3 Times/Day	1 Time /Day	1 Time /Week
High order polynomial	0.85	0.85	0.79	0.78
Linear polynomial	0.90	0.89	0.82	0.73
Difference	0.05	0.04	0.03	0.05
Percentage of difference (difference/high order polynomial)	5.56%	4.49%	3.66%	6.85%

Table 5-4 Comparison between linear and high order polynomial interpolation in the Sick & Elderly SPA model

Sick & Elderly	6 Times/Day	3 Times/Day	1 Time /Day	1 Time /Week
High order polynomial	0.94	0.91	0.72	0.52
Linear polynomial	0.96	0.93	0.72	0.51
Difference	0.02	0.02	0.00	0.01
Percentage of difference (difference/high order polynomial)	2.08%	2.15%	0.00%	1.96%

5.2.4 Normalized cross-correlation at zero lag

The NCCZLs can quantitatively illustrate the similarity of the two sequences of the CBG and the interpolation, which are then compared to demonstrate an optimal MF for a specific SPA.

A cross-correlation function that calculates the NCCZL is a measure of the similarity of two waveforms as a function of a time-lag applied to one of them. Using a normalized cross-correlation function, the sequence will be normalized by subtracting the mean and dividing by the standard deviation at every step, which makes the results comparable among different SPAs. Also, only the cross-correlation value at zero time-lag is considered in the work. The equation for calculating the cross-correlation of signals can be easily found in a signal processing textbook [72]. To emphasize the similarity between the two sequences, the CBG and the interpolation are regulated to zero-mean signals by subtracting corresponding mean value.

In considering the Sick & Elderly SPA with a monitoring frequency of *3 times per day* (see Figure 5-6), the SPA can monitor BG at the six critical points within two days; thereby obtaining a daily representation (see the red dashed line) of the CBG every two days. In this figure, the green line represents the CBG in the first day and the blue line represents that of the second day. Two NCCZLs are calculated between the interpolation and the CBG of the first two days. Another two NCCZLs can be gained in the next two days and so on. Table 5-5 shows NCCZLs of the Sick & Elderly SPA in a six-day simulation scenario. The NCCZL is capable of illustrating to some extent how the interpolation can represent the corresponding CBG. In other words, the NCCZLs show

whether the samples in the MF of *3 times per day* have the ability to properly represent the CBG. The mean and variance of the NCCZLs can further demonstrate this.

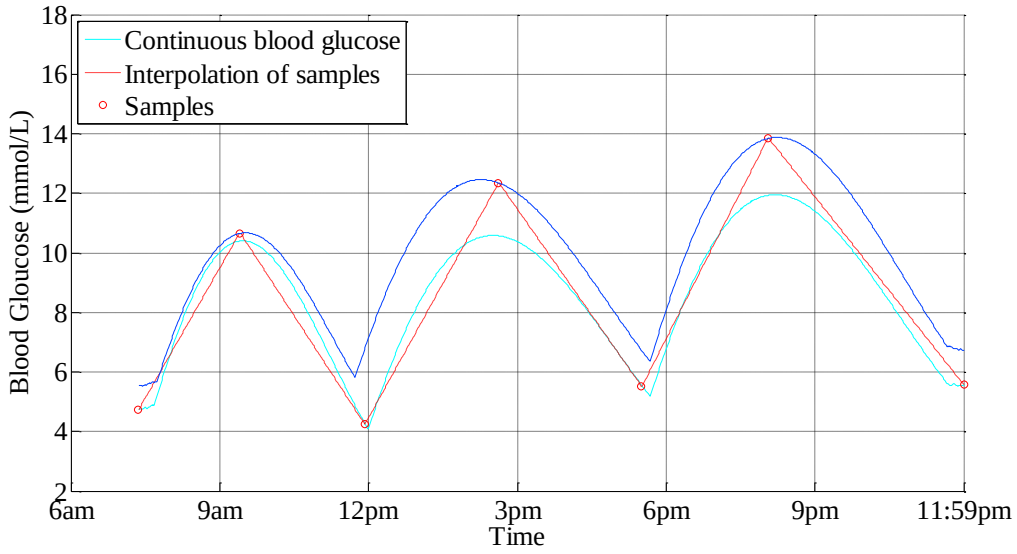


Figure 5-6 NCCZL of the Sick & Elderly SPA with monitoring frequency of 3 times/day

Table 5-5 NCCZLs of the Sick & Elderly SPA in six-day simulation scenario

Factors \ Day	1	2	3	4	5	6
NCCZLs	0.9667	0.9429	0.9555	0.9709	0.8412	0.8529

5.2.5 Average value deviation

We have discussed the NCCZL; however, it can only demonstrate the similarity of the interpolation and the corresponding CBG. Another factor is the deviation between these values, and we use AVD to illustrate this. The rationale for this calculation is similar to that of the NCCZL. Figure 5-7 shows how the AVD is calculated. The green and blue horizontal lines represent the average BG of the first day and the second day, respectively, while the red horizontal line represents the average BG of the interpolation. The deviation between the average values, called the AVD, is also calculated. Table 5-6 shows AVDs of the Sick & Elderly SPA in a six-day simulation scenario. Again, the mean and variance of the AVDs can further demonstrate the deviations.

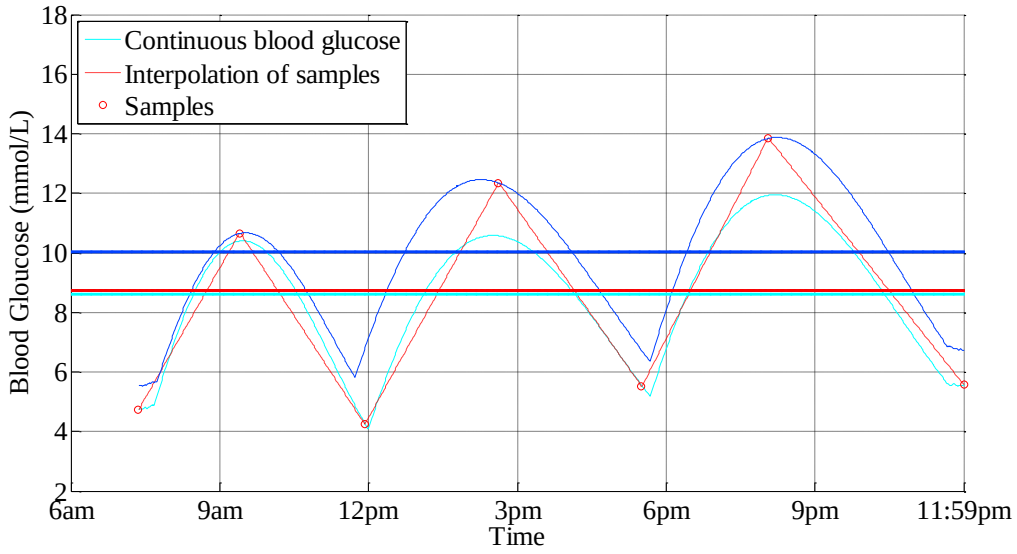


Figure 5-7 AVD of the Sick & Elderly SPA with monitoring frequency of 3 times/day

Table 5-6 AVDs of the Sick & Elderly SPA in six-day simulation scenario

Factors \ Day	1	2	3	4	5	6
AVDs	0.1369	1.2747	0.5260	0.9894	1.0907	0.8446

5.3 Experiments and results

A number of experiments were conducted to simulate nine categories of SPA with different MF. The mean, minimum, maximum, and variance of NCCZLs and AVDs were calculated, to quantitatively characterize to what extent the samples can express the daily pattern of CBG.

In these experiments, we only intended to observe thirty days; however, for the SPA with the MF of *1 time per week*, forty-two days were required to acquire the six critical BG measurements. Therefore, we extended the simulation duration to two months. The configurations for the categories of the SPA have been discussed in section 5.2.2.

5.3.1 Normalized cross-correlation at zero lag

Table 5-7 shows the mean, minimum, maximum, and variance of the NCCZLs in thirty days. In all the experiments, the Sick & Elderly SPA that checked the BG level *1 time per week* reached the worst minimum NCCZLs, which was -0.06. In contrast, the Healthy & Young SPA acquired the best maximum value of 0.98 when it monitored the BG level *6 times per day*.

Figure 5-8 shows the mean of NCCZLs. The highest mean value (0.96) occurred in the Sick & Elderly SPA with an MF of *6 times per day* while the lowest mean value (0.46) occurred in the Sick & Middle-aged SPA who monitored the BG level *1 time per week*. For all types of SPAs, the means of NCCZLs were not significantly different between the MF of *6 times per day* and *3 times per day*. The values ranged from 0.89 (Healthy & Young SPA with an MF of *3 times per day*) to 0.96 (Sick & Elderly SPA with an MF of *6 times per day*). In contrast, the values with respect to the MF of *1 time per day* were lower, which ranged from 0.72 (Sick & Elderly SPA) to 0.85 (Medium &

Middle-aged and Medium & Elderly SPA). The values for the SPA that monitored *1 time per week* were the lowest. The Healthy & Young SPA had the highest value (0.73), while the Sick & Middle-aged SPA had the lowest data (0.46).

Figure 5-9 shows the variance of the NCCZLs. The highest variance (0.0741) was observed in the data for the Sick & Elderly SPA with the MF of *1 time per week* while the lowest variance (0.0002) was observed in the SPA with the MF of *6 times per day*. The variances were very low for all categories of SPA with the MF of *6 times per day* and *3 times per day*. As for the MF of *6 times per day*, the variances observed in the Healthy & Elderly and Sick & Elderly SPAs were low (0.0002) while the Healthy & Young SPA had the greatest variance (0.0026). For the MF of *3 times per day*, the variances ranged from 0.0010 (Healthy & Elderly Patient Agent) to 0.0046 (Healthy & Young Patient Agent). For the SPA with the MF of *1 time per day*, the Sick & Elderly SPA had the greatest variance (0.0389) while the Healthy & Middle-aged SPA had the lowest variance (0.0054). The Sick & Elderly SPA with the MF of *1 time per week* featured the highest variance (0.0741) in the experiments, while the lowest variance (0.0031) observed in the Healthy & Middle-aged SPA with the MF of *1 time per week* was still not considered satisfactory.

In addition, figures from Figure 5-10 to Figure 5-13 illustrate the mean of NCCZLs with error bars. According to the error bars on the figures, the Sick & Elderly SPA with the MF of *6 times per day* had the smallest range (from 0.93 to 0.98) while the same category of SPA with the MF of *1 time per week* had the largest range (from -0.06 to 0.87).

Table 5-7 Various calculations of NCCZLs with different MFs in 30 days

Frequency / Category	6 Times/Day				3 Times/Day			
	Mean	**Min**	**Max**	**Variance**	**Mean**	**Min**	**Max**	**Variance**
Healthy & Young	0.90	0.79	0.98	0.0026	0.89	0.71	0.98	0.0046
Healthy & Middle-aged	0.92	0.85	0.98	0.0013	0.91	0.83	0.96	0.0012
Healthy & Elderly	0.95	0.90	0.97	0.0002	0.93	0.86	0.98	0.0010
Medium & Young	0.91	0.84	0.97	0.0014	0.90	0.77	0.97	0.0028
Medium & Middle-aged	0.94	0.83	0.98	0.0012	0.92	0.79	0.97	0.0019
Medium & Elderly	0.95	0.91	0.98	0.0003	0.92	0.65	0.97	0.0043
Sick & Young	0.91	0.78	0.98	0.0018	0.91	0.81	0.97	0.0017
Sick & Middle-aged	0.94	0.87	0.98	0.0008	0.92	0.83	0.97	0.0013
Sick & Elderly	0.96	0.93	0.98	0.0002	0.93	0.84	0.97	0.0011

Table 5-7 Various calculations of NCCZLs with different MFs in 30 days (Continued)

Frequency / Category	1 time/Day				1 time /Week			
	Mean	**Min**	**Max**	**Variance**	**Mean**	**Min**	**Max**	**Variance**
Healthy & Young	0.83	0.64	0.93	0.0056	0.73	0.58	0.82	0.0032
Healthy & Middle-aged	0.84	0.66	0.94	0.0054	0.58	0.48	0.69	0.0031
Healthy & Elderly	0.81	0.43	0.95	0.0125	0.60	0.41	0.73	0.0068
Medium & Young	0.81	0.59	0.95	0.0088	0.62	0.42	0.79	0.0079
Medium & Middle-aged	0.85	0.68	0.93	0.0059	0.71	0.61	0.82	0.0040
Medium & Elderly	0.85	0.58	0.97	0.0098	0.53	0.24	0.77	0.0241
Sick & Young	0.77	0.27	0.90	0.0209	0.56	0.42	0.68	0.0061
Sick & Middle-aged	0.81	0.64	0.96	0.0065	0.46	0.06	0.76	0.0404
Sick & Elderly	0.72	0.26	0.96	0.0389	0.50	-0.06	0.87	0.0741

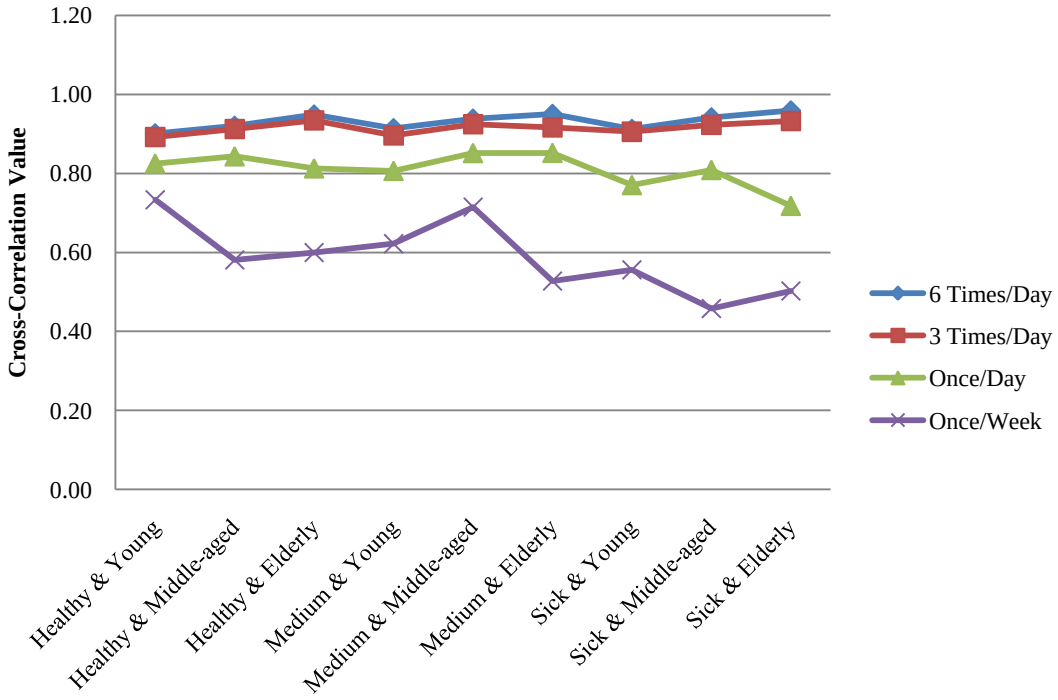


Figure 5-8 Mean of the NCCZLs

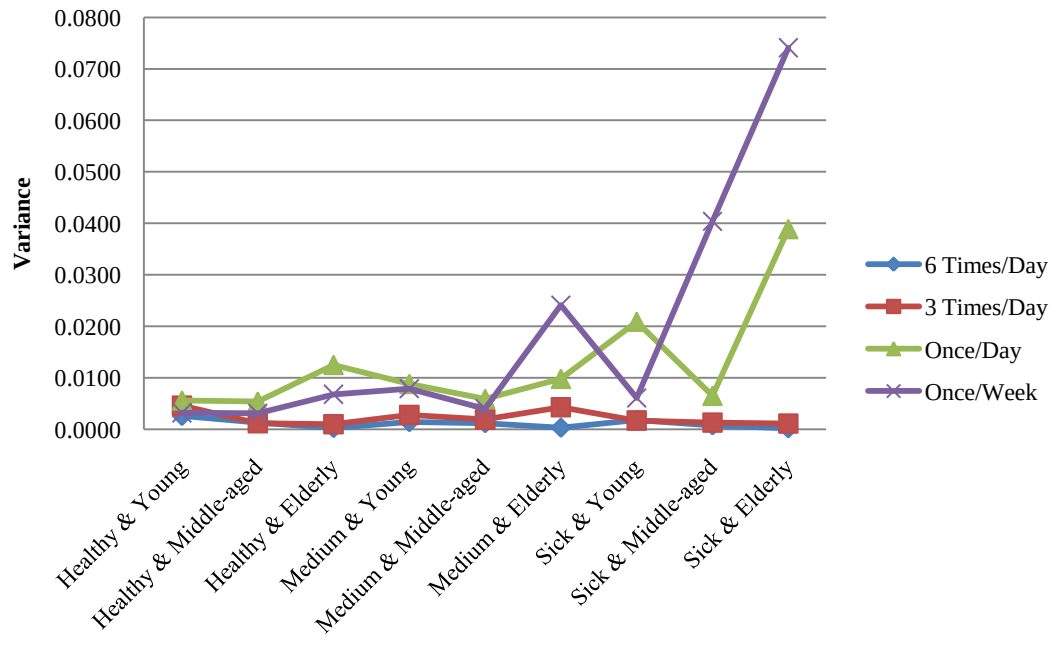


Figure 5-9 Variances of the NCCZLs

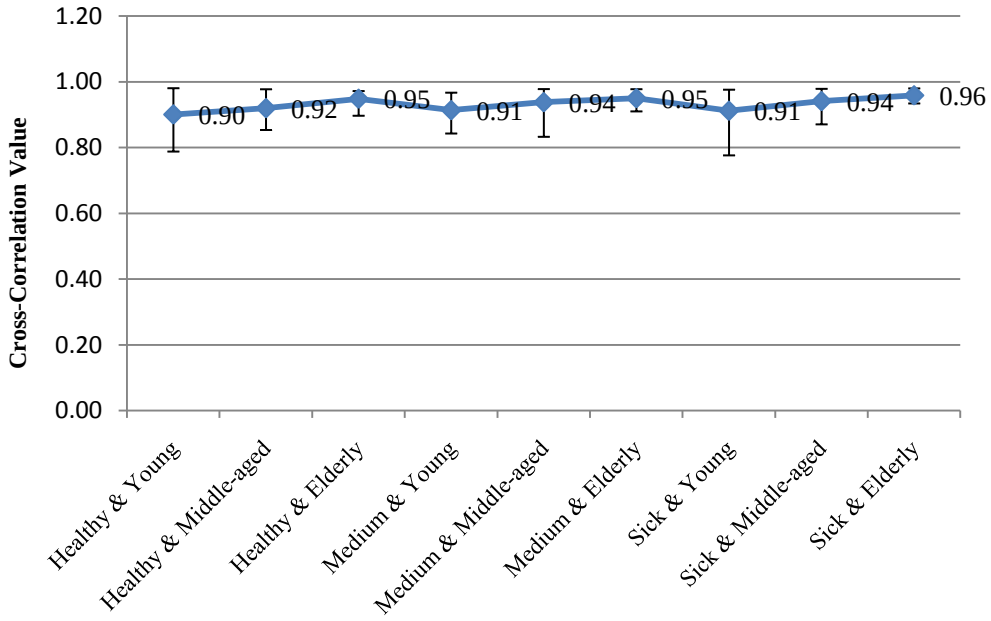


Figure 5-10 Mean of NCCZLs with the MF of 6 times/day

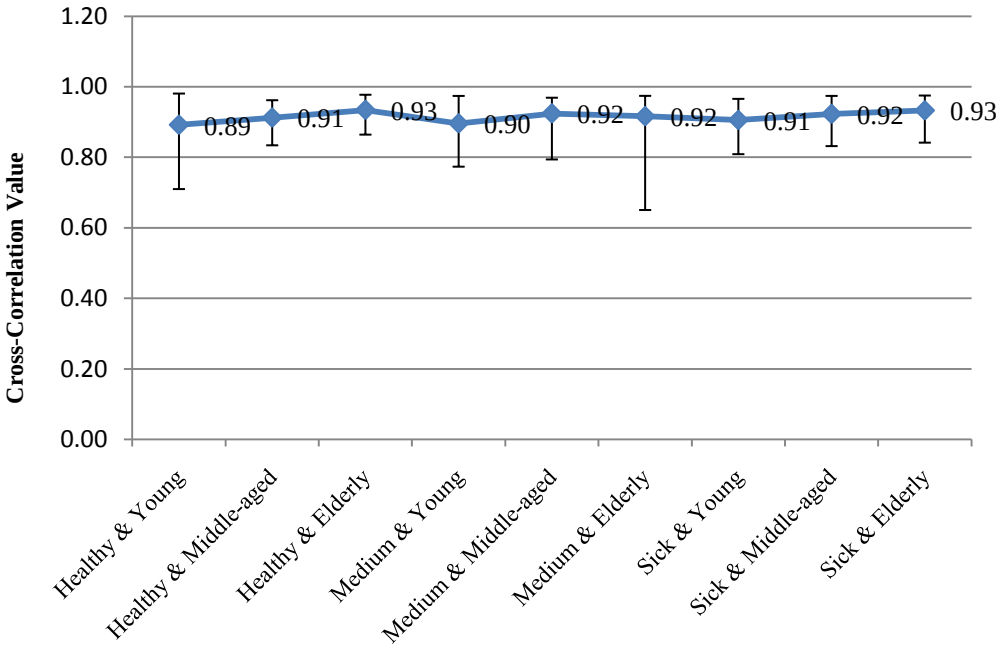


Figure 5-11 Mean of NCCZLs with the MF of 3 times/day

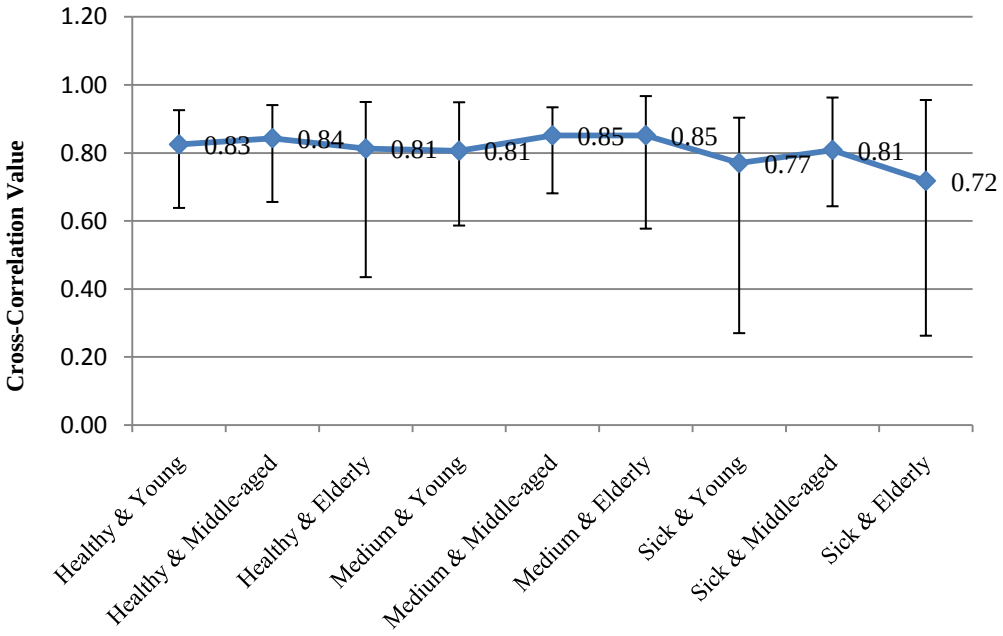


Figure 5-12 Mean of NCCZLs with the MF of 1 time/day

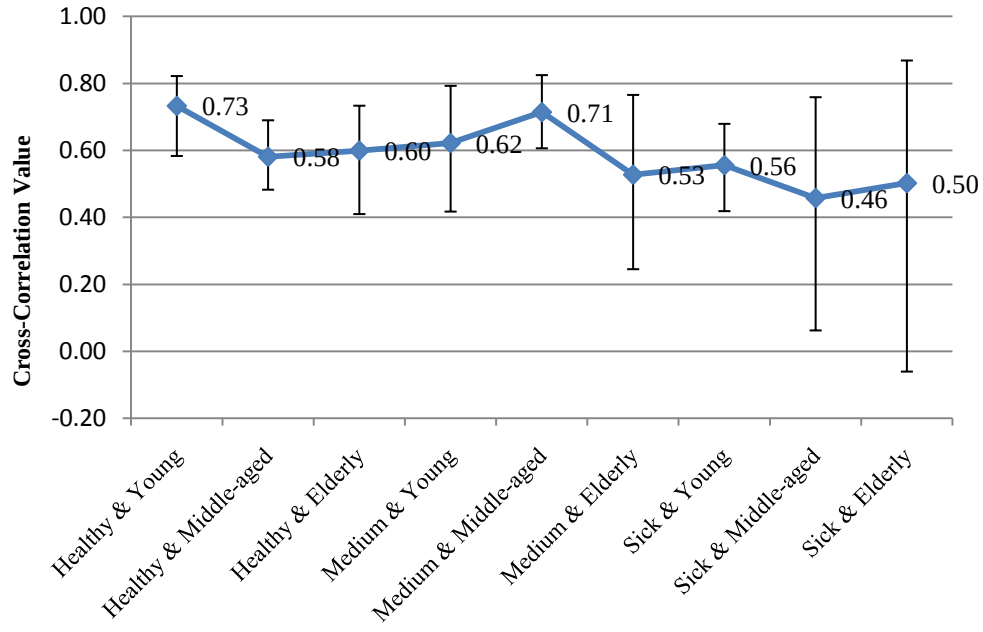


Figure 5-13 Mean of NCCZLs with the MF of 1 time/week

5.3.2 Average deviation value

Table 5-8 shows the mean, minimum, maximum, and variance of the AVDs in thirty days. The Sick & Young SPA with the MF of *3 times per day*, Medium & Young SPA with the MF of *1 time per day*, and Medium & Elderly SPA with the MF of *1 time per week* reached an ideal minimum AVDs of 0. In contrast, the Sick & Middle-aged SPA acquired the worst maximum value of 14.21 when it monitored the BG level *1 time per week*.

From Figure 5-14, we can see that all the SPAs with an MF of *6 times per day*, *3 times per day* and even *1 time per week* had a satisfactory mean of AVDs. The highest mean value of 0.95 occurred in the Sick & Middle-aged SPA with an MF of *1 time per week*, while the lowest mean value (0.43) occurred in the Medium & Elderly SPA that monitored the BG level *6 times per day*. Similar patterns could also be seen in the variance of AVDs (see Figure 5-15). The Sick & Middle-aged SPA with the MF of *1 time per week* had the highest variance of 20.0421.

Figures from Figure 5-16 to Figure 5-19 illustrate the mean of AVDs with error bars. From the error bars on Figure 5-16 and Figure 5-17, we can see that the mean values of all the SPAs with the MF of *6 times per day* and *3 times per day* were very stable. Therefore, in any case, it was not necessary to monitor BG *6 times per day*. Even the performance of the SPAs with the MF of *1 time per day* was acceptable (see Figure 5-18). The only concerns were with the SPAs with the MF of *1 time per week*, except the Healthy & Young and Healthy & Middle-aged SPAs (see Figure 5-19).

Table 5-8 Various calculations of AVDs with different MFs in 30 days

Frequency / Category	6 Times/Day				3 Times/Day			
	Mean	**Min**	**Max**	**Variance**	**Mean**	**Min**	**Max**	**Variance**
Healthy & Young	0.48	0.33	0.77	0.0106	0.50	0.02	1.16	0.0667
Healthy & Middle-aged	0.50	0.33	0.74	0.0129	0.56	0.01	1.19	0.1267
Healthy & Elderly	0.40	0.28	0.65	0.0073	0.51	0.03	1.06	0.0925
Medium & Young	0.44	0.27	0.64	0.0090	0.54	0.06	1.33	0.0953
Medium & Middle-aged	0.55	0.39	0.71	0.0048	0.58	0.05	1.31	0.0941
Medium & Elderly	0.43	0.29	0.64	0.0087	0.58	0.02	1.32	0.1402
Sick & Young	0.61	0.33	1.06	0.0309	0.57	0.00	1.69	0.1448
Sick & Middle-aged	0.59	0.36	0.88	0.0216	0.55	0.01	1.42	0.0956
Sick & Elderly	0.49	0.34	0.75	0.0106	0.51	0.01	1.27	0.1325

Table 5-8 Various calculations of AVDs with different MFs in 30 days (Continued)

Frequency / Category	1 Time/Day				1 Time/Week			
	Mean	**Min**	**Max**	**Variance**	**Mean**	**Min**	**Max**	**Variance**
Healthy & Young	0.55	0.03	1.42	0.1225	1.07	0.09	2.22	0.4351
Healthy & Middle-aged	0.54	0.06	1.35	0.1461	0.54	0.02	1.58	0.1780
Healthy & Elderly	0.83	0.08	2.63	0.3456	2.55	0.25	6.36	2.4582
Medium & Young	0.61	0.00	1.82	0.2187	2.26	0.48	4.54	1.5243
Medium & Middle-aged	0.71	0.03	2.27	0.2567	2.14	0.04	7.13	2.7185
Medium & Elderly	0.64	0.01	2.74	0.3343	2.88	0.00	6.00	2.5908
Sick & Young	0.87	0.11	2.39	0.3404	2.03	0.27	5.48	1.9289
Sick & Middle-aged	0.95	0.03	3.05	0.7011	7.63	0.64	14.21	20.0421
Sick & Elderly	1.06	0.09	3.87	0.7249	4.42	0.17	14.01	12.1519

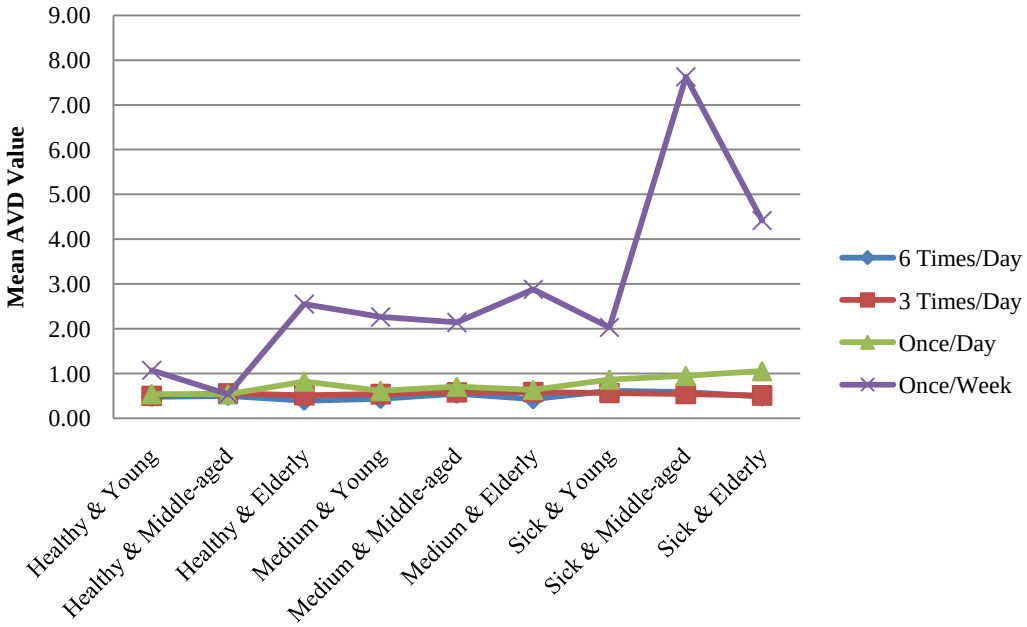


Figure 5-14 Mean of AVDs

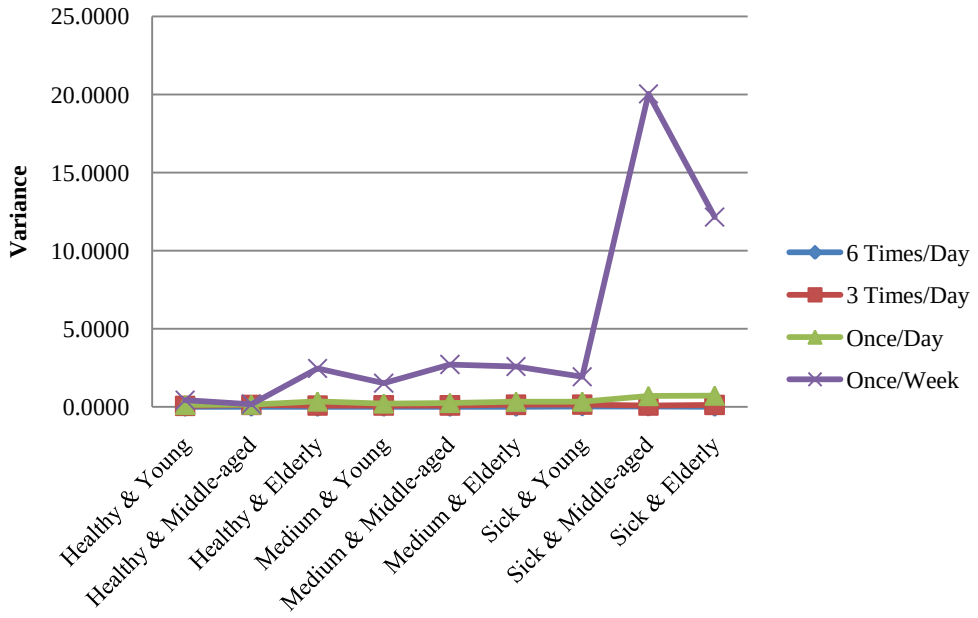


Figure 5-15 Variance of AVDs

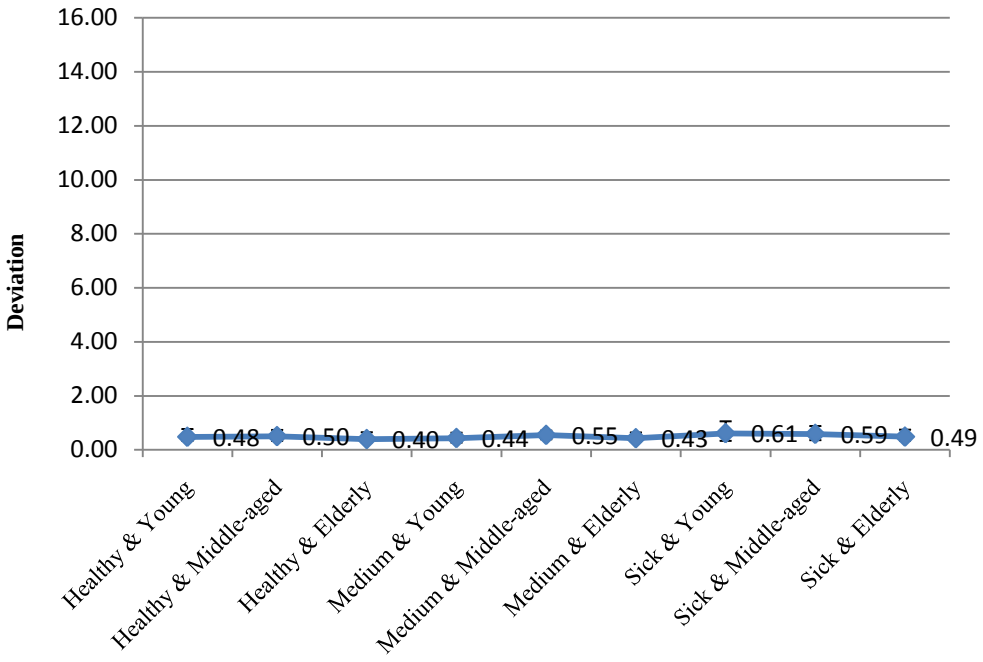


Figure 5-16 Mean of AVDs with the MF of 6 times/day

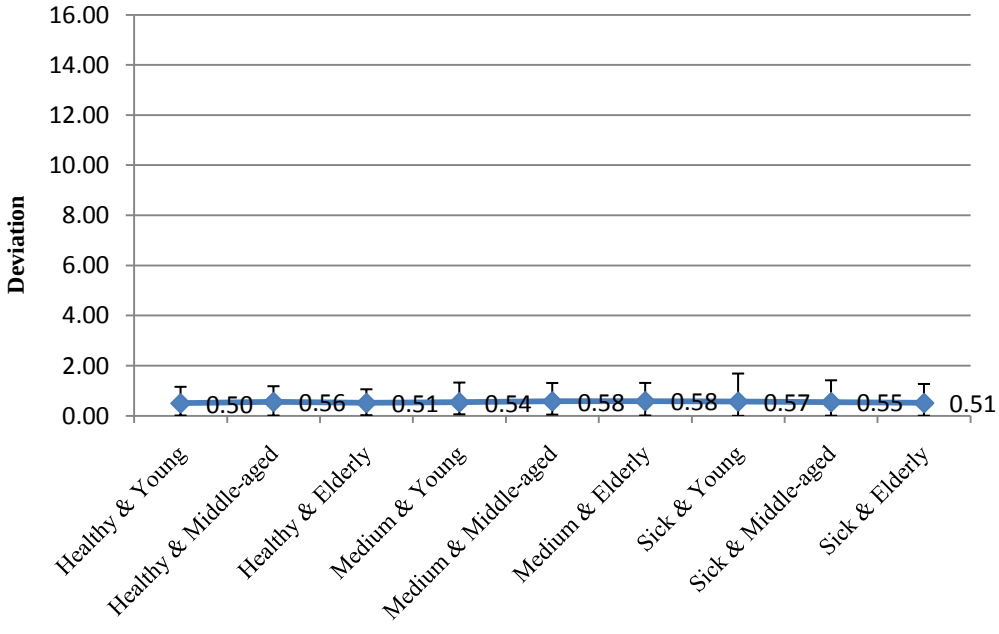


Figure 5-17 Mean of AVDs with the MF of 3 times/day

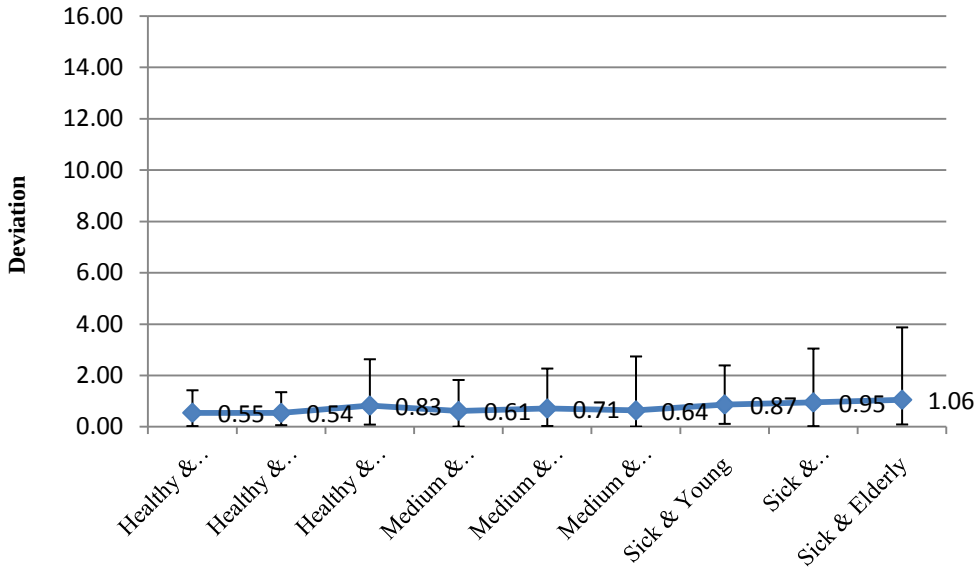


Figure 5-18 Mean of AVDs with the MF of 1 time/day

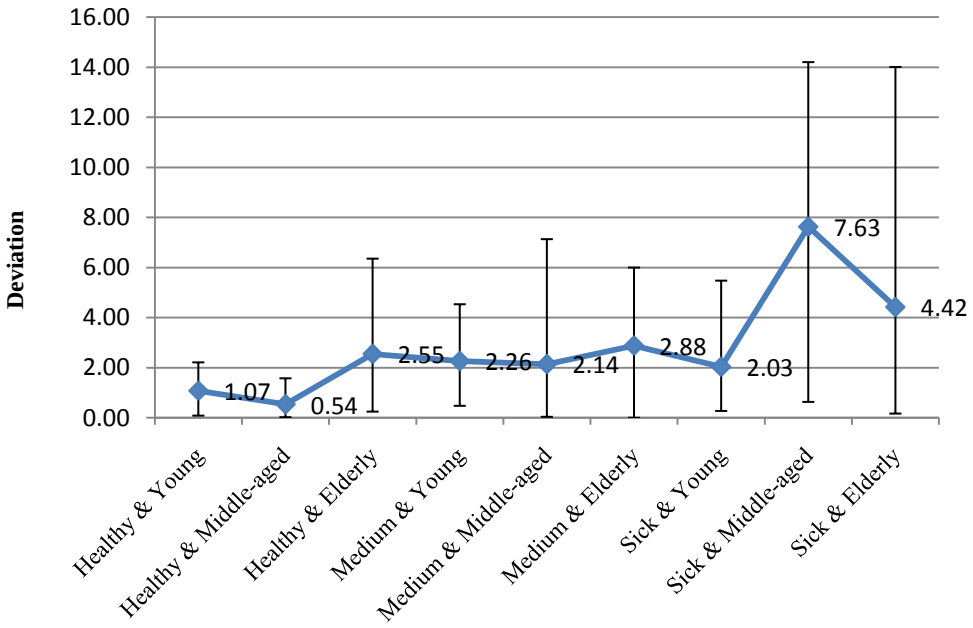


Figure 5-19 Mean of AVDs with the MF of 1 time/week

5.4 Summary

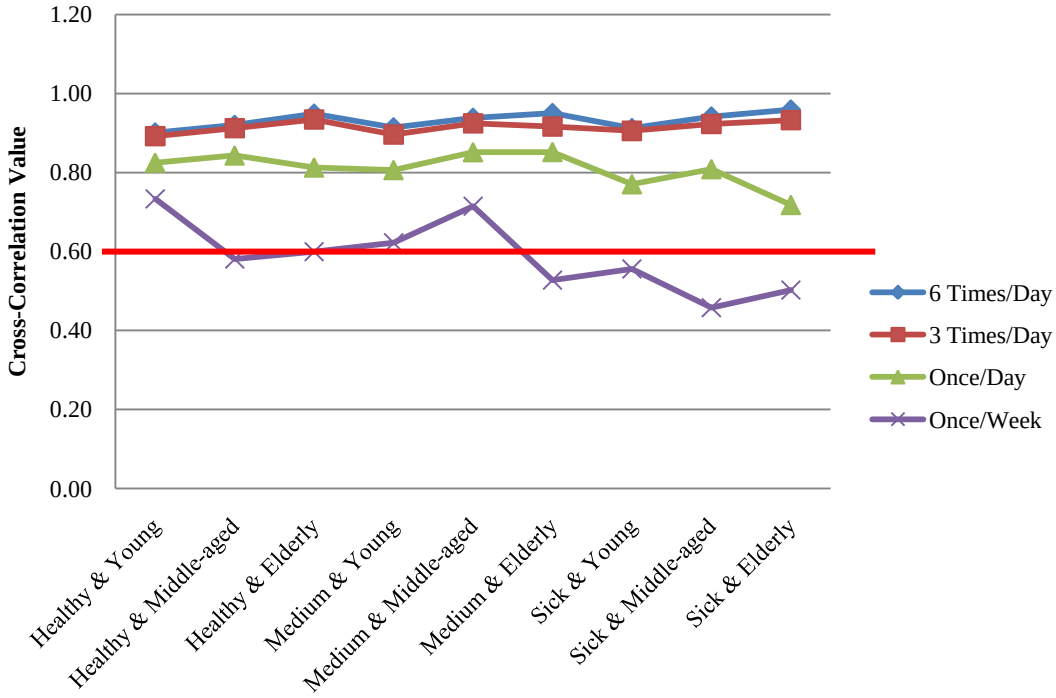
SMBG is a highly recommended treatment for diabetic patients; therefore it is developing an increasingly higher cost for both the healthcare system and individuals. Discomfort and potential infection when patients' fingers are pricked are also factors in SMBG. Therefore, it is increasingly necessary to guide patients with an optimal frequency of sampling in order to reduce both cost and discomfort. The conventional method of RCT *in vivo* has obvious disadvantages, such as it being time consuming, the huge cost associated with it and inherent difficulties in studying unique events. Therefore, in this chapter, we propose a novel method of calculating NCCZLs and AVDs and observing their mean and variance to examine the effectiveness of different levels of MFs *in silico*.

NCCZLs illustrate the similarity between the interpolation and the CBG, while AVDs show their deviation, a combination of which can adequately demonstrate how well the samples can represent the CBG. Furthermore, the mean and variance of the two factors facilitate a general understanding of the relationship between samples and the actual signal in certain period of time.

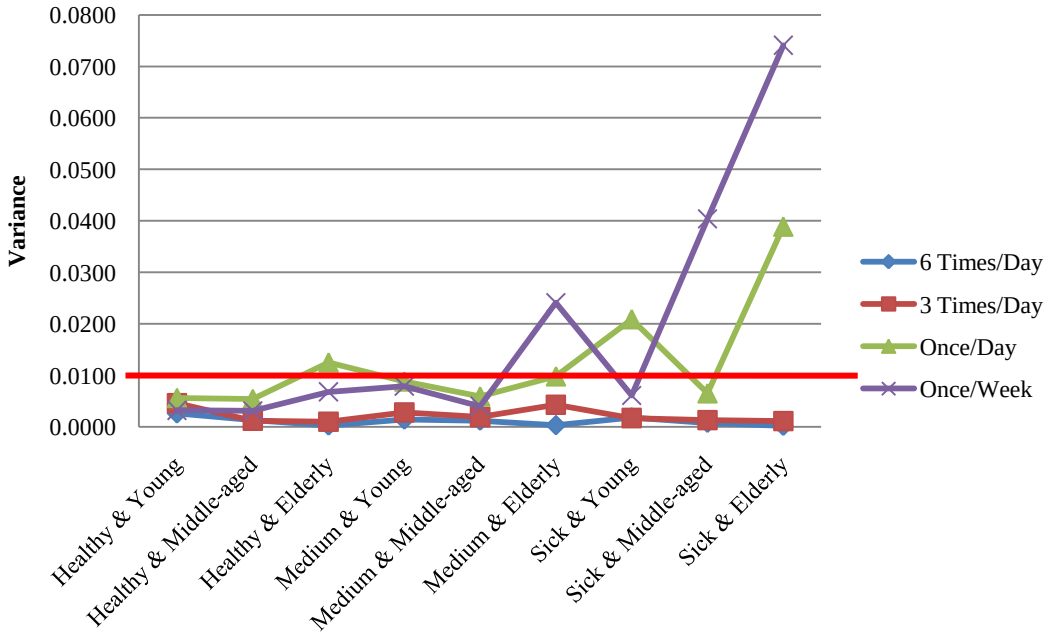
It should be noted that, judging an optimal MF depends on appropriate thresholds. In other words, it depends on how much effort and expense patients are willing to expend. In this work, the selected thresholds are shown in Table 5-9. The values are marked as red solid lines in Figure 5-20.

Table 5-9 Thresholds of mean and variance of NCCZLs and AVDS

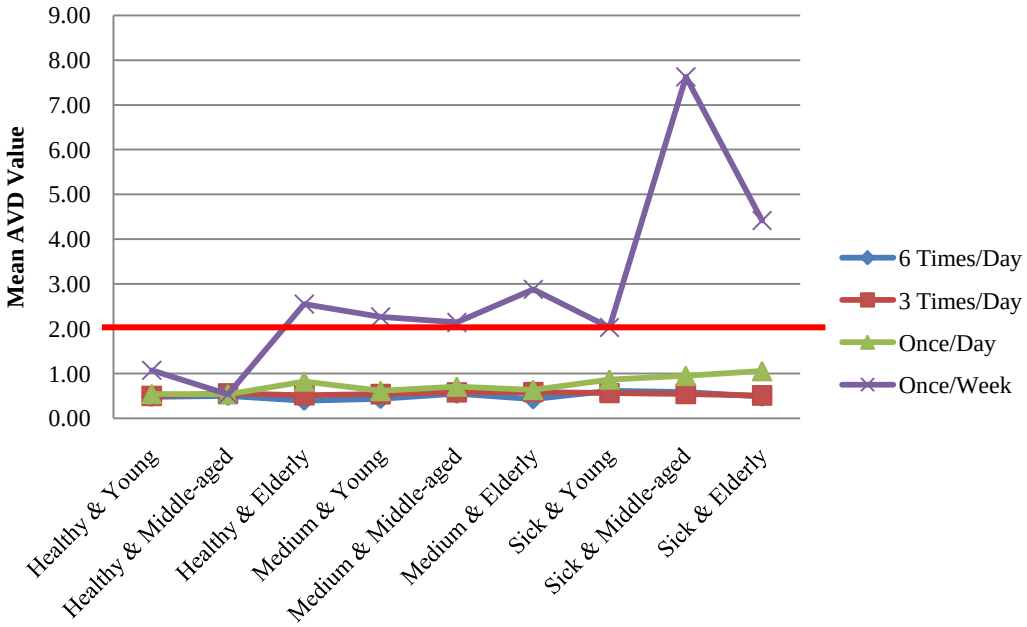
	NCCZL	AVD
Mean	0.60	2.0
Variance	0.0100	5.0000


1.20
1.00
0.80
0.60
0.40
0.20
0.00
Cross-Correlation Value
Healthy & Young
Healthy & Middle-aged
Healthy & Elderly
Medium & Young
Medium & Middle-aged
Medium & Elderly
Sick & Young
Sick & Middle-aged
Sick & Elderly
6 Times/Day
3 Times/Day
Once/Day
Once/Week

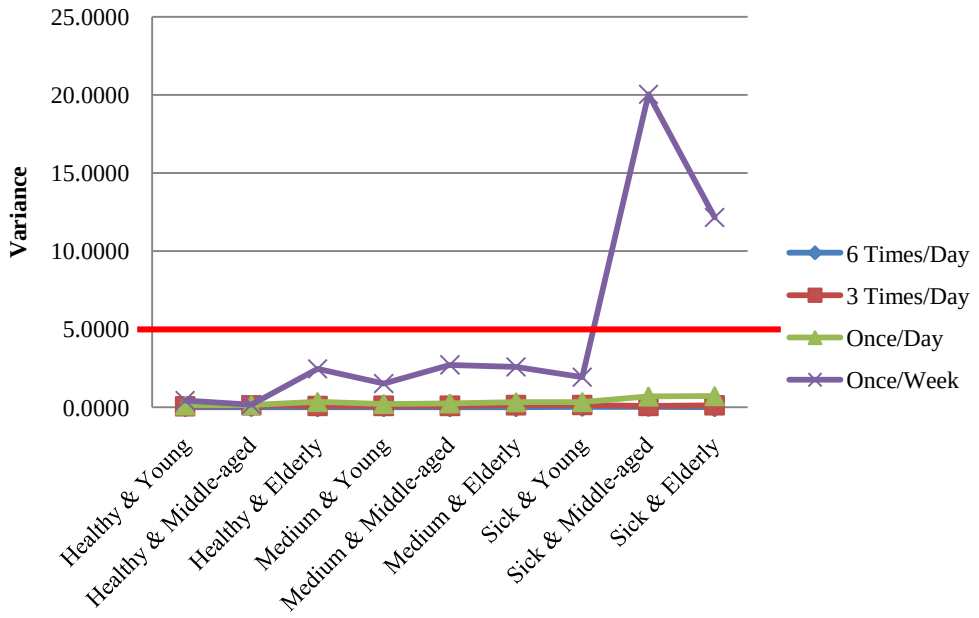
(a)


0.0800
0.0700
0.0600
0.0500
0.0400
0.0300
0.0200
0.0100
0.0000
Variance
Healthy & Young
Healthy & Middle-aged
Healthy & Elderly
Medium & Young
Medium & Middle-aged
Medium & Elderly
Sick & Young
Sick & Middle-aged
Sick & Elderly
6 Times/Day
3 Times/Day
Once/Day
Once/Week

(b)



(c)



(d)

Figure 5-20 Mark lines of thresholds of (a) Mean of the NCCZLs (b) Variances of the NCCZLs (c) Mean of the AVDs (d) Variances of the AVDs

For the mean of the NCCZLs, higher value is ideal, because this indicates a greater similarity. By contrast, a lower mean value of AVDs indicates a greater similarity, as well. Variance is always expected to be lower, as this indicates greater stability. An valuation table (Table 5-10) was created in order to visualize this concept. The first two columns show SPAs with a specific MF, and the third column to the sixth column shows the four factors. The last column illustrates the final evaluation result. Tick marks indicate that the evaluation is qualified based on the selected thresholds, while cross marks indicate the opposite. As long as one of the factors is not satisfactory, the overall evaluation is not qualified. For instance, the Healthy & Middle-aged SPA with the MF of *1 time per week* did not qualify the mean of NCCZLs. Although it satisfied the other factors, the overall result was not qualified, which meant the MF of *1 time per week* was not the optimal frequency for the Healthy & Middle-aged SPA. Instead, it should adopt the closest satisfactory frequency: *1 time per day*. Table 5-10 gives an optimal frequency of sampling for each SPA.

At the end of the chapter, we emphasize that by introducing the signal technique we want to build a base line of MFs for different SPA *in silico* rather than construct a guideline for a specific individual *in vivo*. However, this may assist people to determine an optimal frequency for sampling based on their particular condition.

Table 5-10 Evaluation table

Categories	Monitoring frequency	NCCZLs		AVDs		Overall
		Mean	Variance	Mean	Variance	
Healthy & Young	6 times/day	✓	✓	✓	✓	✓
	3 times/day	✓	✓	✓	✓	✓
	1 time/day	✓	✓	✓	✓	✓
	1 time/week	✓	✓	✓	✓	✓
Healthy & Middle-aged	6 times/day	✓	✓	✓	✓	✓
	3 times/day	✓	✓	✓	✓	✓
	1 time/day	✓	✓	✓	✓	✓
	1 time/week	×	✓	✓	✓	×
Healthy & Elderly	6 times/day	✓	✓	✓	✓	✓
	3 times/day	✓	✓	✓	✓	✓
	1 time/day	✓	×	✓	✓	×
	1 time/week	×	✓	×	✓	×
Medium & Young	6 times/day	✓	✓	✓	✓	✓
	3 times/day	✓	✓	✓	✓	✓
	1 time/day	✓	✓	✓	✓	✓
	1 time/week	✓	✓	×	✓	×
Medium & Middle-aged	6 times/day	✓	✓	✓	✓	✓
	3 times/day	✓	✓	✓	✓	✓
	1 time/day	✓	✓	✓	✓	✓
	1 time/week	✓	✓	×	✓	×
Medium & Elderly	6 times/day	✓	✓	✓	✓	✓
	3 times/day	✓	✓	✓	✓	✓
	1 time/day	✓	✓	✓	✓	✓
	1 time/week	×	×	×	✓	×
Sick & Young	6 times/day	✓	✓	✓	✓	✓
	3 times/day	✓	✓	✓	✓	✓
	1 time/day	✓	×	✓	✓	×
	1 time/week	×	✓	×	✓	×
Sick & Middle-aged	6 times/day	✓	✓	✓	✓	✓
	3 times/day	✓	✓	✓	✓	✓
	1 time/day	✓	✓	✓	✓	✓
	1 time/week	×	×	×	×	×
Sick & Elderly	6 times/day	✓	✓	✓	✓	✓
	3 times/day	✓	✓	✓	✓	✓
	1 time/day	✓	×	✓	✓	×
	1 time/week	×	×	×	×	×

CHAPTER 6

THE MULTI-AGENT SYSTEM

The Patient Agent, which represents one of the most important components in the healthcare system, the patient, has been discussed in the previous chapters. The efficiency of various lifestyles, the self-awareness and the treatment of SMBG were evaluated in a micro scope. In this chapter, we propose a multi-agent system by introducing other healthcare components, so that other insights such as the healthcare quality, cost and performance can be observed in a macro scope. However, we only present a design of the multi-agent system so far. Further experiments will be conducted in the future.

In this chapter, the system architecture is described first, and then agents are illustrated in detail.

6.1 System architecture

Figure 6-1 shows the system architecture. The multi-agent healthcare system has ten kinds of software agents, which are: Interface Agent, Administrative Agent, Report Agent, Patient Agent, Healthy Person Agent, Physician Agent, Kidney/Dialysis Ward Agent, Eye Ward Agent, Heart/Stroke Ward Agent, Foot Ward Agent, and Emergency Agent. Four TEEMA platforms are used to organize these agents: Administrative Platform, Population Platform, Physician Platform and Hospital Platform. Specifically, the Interface Agent, the Administrative Agent and the Report Agent are designated in the Administrative Platform while the Patient Agents and Healthy Person Agent are hosted by the Population Platform. The Hospital Platform hosts the Kidney/Dialysis Ward Agent,

the Eye Ward Agent, the Heart/Stroke Ward Agent and the Emergency Agent. The Physician Agents reside on the Physician Platform.

The user can input information to configure the system through the Interface Agent. The Administrative Agent supervises the system and the Report Agent presents a statistical report. The Patient Agent, the Healthy Person Agent, and the Physician Agent represent a diabetic patient, a healthy person, and a diabetes specialist, respectively. The ward agents mimic their corresponding wards and the Emergency Agent represents an emergency department in a hospital. In addition, the system can have multiple hospital platforms to simulate that a city may have more than one hospital.

The Interface Agent and the Administrative Agent are the first two agents initiated in the system. The Administrative Agent then generates the other agents with respect to the system configuration received from the Interface Agent. The Interface Agent, the Administrative Agent and the Report Agent stay in the Administrative Platform, and other agents immigrate to a specific platform where they should reside.

Due to their self-awareness, Patient Agents may go to see Physician Agents. When a Patient Agent visits a Physician Agent, the Physician Agent may diagnose and charge the Patient Agent based on its knowledge-based rules. If the Patient Agent does not have any problems, the Physician Agent will allow it to continue its previous lifestyle without modification. However, if the Patient Agent has some problems, the Physician Agent may give it a prescription, such as eating food with lower GI and improving the intensity of exercise or medication, or the Physician Agent might refer it to a ward agent (shown by the dashed bidirectional line in Figure 6-1) in the hospital platform, and the ward agent may keep the Patient Agent in the hospital for a specific period of time. The

Patient Agents may also faint and go to the Emergency Agent directly, in which case the Emergency Agent will either look after it or refer it to a ward agent. Meanwhile the Healthy Person Agent representing a person without diabetes, may occasionally occupy the healthcare resources such as seeing a Physician Agent, staying in the hospital and running to the EA. Whenever Patient Agents and Healthy Person Agents use the healthcare resources, there will be a charge. When the simulation is finished, Physician Agents, ward agents, and the Emergency Agent will present statistical reports (e.g. times of receiving a Patient Agent and corresponding fees) to the Report Agent. The Report Agent collects and analyses the data to generate a final report, and then sends it to the Interface Agent so that users can see it.

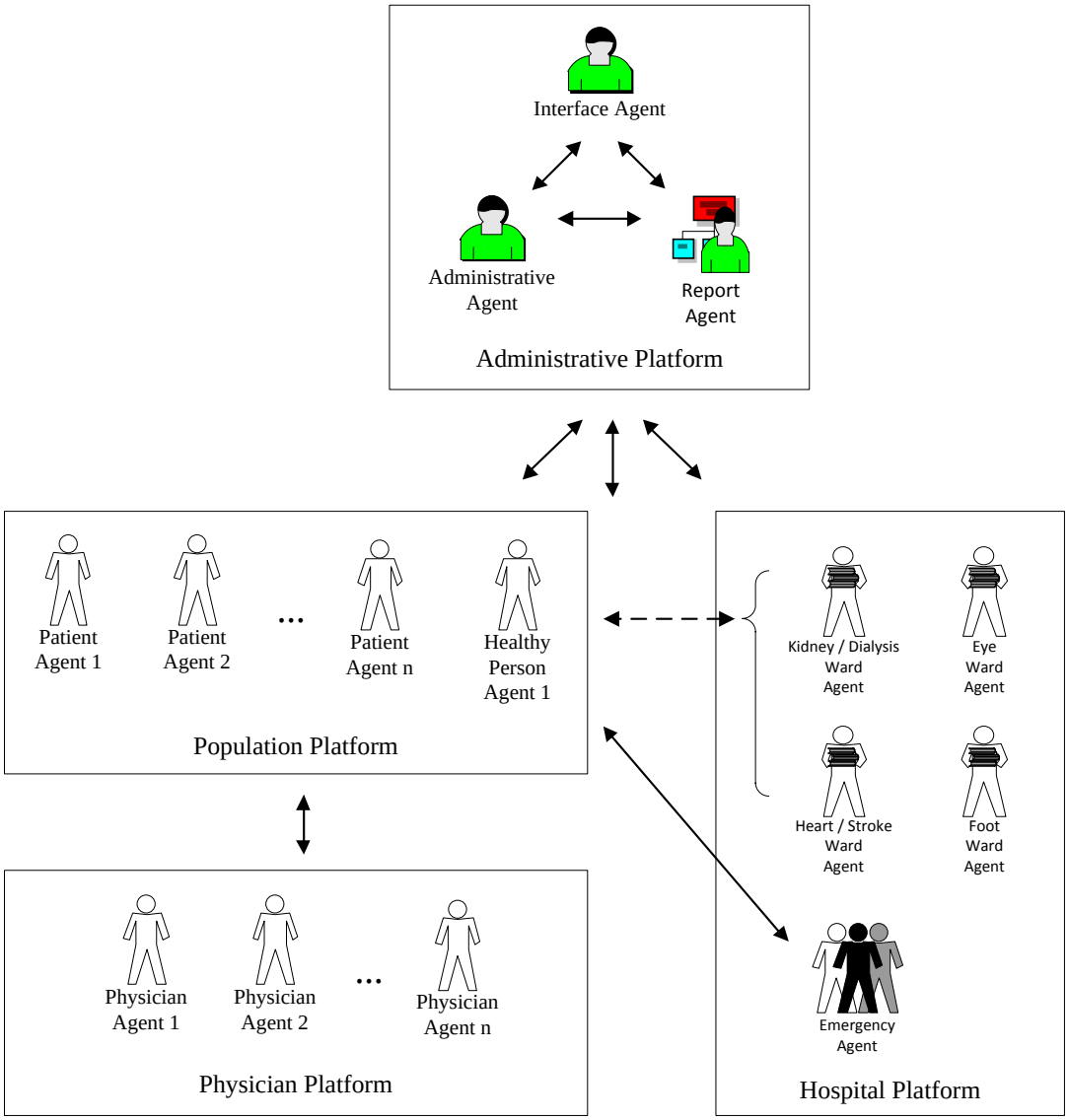


Figure 6-1 Architecture of the multi-agent system

6.2 Agent description

6.2.1 Interface Agent

The Interface Agent, as the name represents, provides a GUI for a user to input information for configuring the system.

6.2.2 Administrative Agent

The Administrative Agent is a stationary agent residing in the Administrative Platform. The Administrative Agent has a list of address of all agents so that agents can reach each other through consulting it. It is the first agent generated by the system and its name and address is fixed based on the computer name and IP address. The Administrative Agent's name and address is public and known by all agents that are generated later. Each agent registers or updates its information to the Administrative Agent when it is created, destroyed, or its status changes. For instance, when a Patient Agent is generated, it will register its information to the Administrative Agent. Also, a Patient Agent may pass away; or a Physician Agent may retire, leave the hospital or transfer to another hospital, in which case the Administrative Agent will delete or update its list. The Administrative Agent is also a date coordinator. It controls the date in order to schedule all agents. When an agent finishes a single simulation day, it sends a message to the Administrative Agent. The Administrative Agent will notify all the agents when all agents finish the current simulation day. The main functions of the Administrative Agent are listed below.

- Has an address list of all agents
- Acts as a date coordinator

- Supervises the system

6.2.3 Report Agent

The Report Agent is a stationary agent. It is considered as a manager agent and stays in the Administrative Platform. It is responsible for collecting statistical data from other agents such as Physician Agents, ward agents or the Emergency Agent. It presents the data to the Interface Agent after the simulation is completed. The main functions are as follows.

- Collects healthcare information such as healthcare quality and cost
- Analyzes data and generates final report

6.2.4 Patient Agent

The Patient Agents are mobile agents that represent Type 2 diabetic patients. With the autonomy of a software agent, it can migrate to the Physician Platform to visit a Physician Agent. It can also travel to hospital platform and be hospitalized if referred by a Physician Agent. In an emergency situation, it may faint and go to the Emergency Agent in the hospital platform. It can also act with respect to a prescription from a Physician Agent. The detailed design has been discussed in CHAPTER 3 and CHAPTER 4.

The Patient Agent is one of the most important subjects that the system contains. In this study, the distribution of age levels and health status of these agents are considered. We can scale down the number and simulate the population in a province or a city. Such distribution information can be found in literatures. The age distribution of people with diabetes in Saskatchewan, for instance, is shown in Table 6-1 [73]. Also, a normalized

distribution of health status is expected. In addition, healthy people are mapped by a Healthy Person Agent since they may use healthcare resource occasionally.

Table 6-1 Persons with diabetes in Saskatchewan

Persons with diabetes	First nations (n = 4,061)	Number excluding first nations (n = 41,655)	Total number (n=45,716)
Gender			
male	1,677 (41.3%)	22,131 (53.1%)	23,808 (52.1%)
female	2,384 (58.7%)	19,524 (46.9%)	21,908 (47.9%)
Average age	48.7	61.4	60.3
Age Distribution			
0-39 years	1,116 (27.5%)	4,936 (11.8%)	6,052 (13.2%)
40-64 years	2,296 (56.5%)	15,990 (38.4%)	18,286 (40.0%)
65+ years	649(16.0%)	20,729 (49.8%)	21,378 (46.8%)

Main functions of the Patient Agent are listed here.

- Generates continuous blood glucose based on a lifestyle
- Monitors its blood glucose in a specific frequency
- Visits a Physician Agent
- Adopts a lifestyle prescribed by a Physician Agent
- Goes to the diabetes ward according to the diagnosis of a Physician Agent
- Visits an Emergency Agent

6.2.5 Healthy Person Agent

Healthy Person Agents are mobile agents and they simulate people without diabetes who may occasionally occupy healthcare resources such as the emergency department. They carry information such as age level and possibility of seeing a physician or running to the emergency department. The age levels are young, middle and

elderly, and it is reasonable to assume that the older a Healthy Person Agent is, the greater the likelihood of it using healthcare resources.

6.2.6 Physician Agent

The Physician Agent is a mobile agent and can travel between the Physician Platform and the Hospital Platform. It has rule-based knowledge. The following list shows its main functions.

- Diagnoses a Patient Agent to determine whether it experiences any diabetes-related problems such as hyperglycemia or hypoglycemia
- Prescribes according to its diagnosis
- Charges Patient Agents based on prescriptions
- Looks after Healthy Person Agents who visit it and charges them
- Calculates times of the Patient Agent's visit
- Calculates diagnostic times of hyperglycemia, hypoglycemia, or no major problems
- Calculates cost for diagnosis and prescription
- Informs a statistic report to the Report Agent

6.2.7 Ward agents

There are four ward agents; namely, the Kidney/Dialysis Ward Agent, the Eye Ward Agent, the Heart/Stroke Ward Agent and the Foot Ward Agent. They reside in a Hospital Platform. They can hospitalize Patient Agents that are referred by a Physician Agent or an Emergency Agent. When Patient Agents are hospitalized, ward agents regulate their behaviour such as food consumption, exercise, and meal schedule, or

prescribe medicine for them. There will also be a charge for the Patient Agent according to the period of hospitalization. Ward agents also schedule hospital resources such as hospital beds and Physician Agents. There may not be beds available or enough Physician Agents in the ward for Patient Agents, so the ward agents may call Physician Agents from the Emergency Agent or refer some Patient Agents to other hospitals. At the end of the simulation, they generate a statistical report for the Report Agent such as the usage of the ward, the occupation of Physician Agents, the number of Patient Agents visiting and the cost. Main functions of ward agents are as follows.

- Hospitalizes, treats and charges a Patient Agent
- Schedules the hospital beds in the ward
- Schedules the Patient Agents in the ward
- Call Physician Agents from the Emergency Agent when necessary and applicable
- Refers Patient Agents to other hospitals when necessary
- Calculates the bed occupation, number of Patient Agent and Healthy Person Agent visits and cost
- Sends a statistical report to the Report Agent

6.2.8 Emergency Agent

The Emergency Agent resides in the hospital platform and looks after Patient Agents and Healthy Person Agents. When Patient Agents go to the Emergency Agent, it will treat them quickly and then refer them to a ward agent. When the visiting agents are Healthy Person Agents, it will help them and then discharge them directly since this system only hospitalizes Patient Agents.

CHAPTER 7

CONCLUSIONS AND FUTURE WORKS

This thesis examines the CPA and the SPA models of a diabetic patient's blood glucose levels within a mobile agent environment. The efficiency of various lifestyles, the self-awareness and SMBG are evaluated through the two models in a micro scope. Furthermore, the multi-agent system is developed by introducing other healthcare components in order to allow the observation of factors such as the healthcare quality, cost and performance in a macro scope.

The CPA, or controlled patient agent, incorporates the Ackerman model and the RW model in the mobile agent environment. The name of the CPA does not have a special meaning, but only comes from comparison with the SPA (self-aware patient agent) model that is characterized by self-awareness. The CPA enhanced the Ackerman model in two respects. The first is to extend it into nighttime by introducing the RW model. The second improvement is achieved by incorporating a statistical noise component, which captures stochastic human behaviours. Because of the integration of the Ackerman model and the RW model, the CPA is capable of transferring major influential parameters, including food consumption, intensity of exercise and medication, and meal schedule, into CBG levels. A number of experiments are conducted in eleven scenarios of different lifestyles that refer to diabetes treatments recommended by CDA. The simulation results demonstrate how the patient's lifestyle can influence the control of blood glucose levels by counting the times the results fell out of the target range. The major observations from these experiments illustrate that the model can adequately represent typical diabetic

patients. This model can help patients explore their prognosis if they are not meticulous in controlling their blood glucose levels.

Based on the CPA, the SPA further assimilates a BG sensor *in silico* and a reasoning model of changing behaviours, which is analogous to the human patient pricking his/her finger and using a drop of blood to measure their own blood glucose level and then respond to the result. The SPA model also integrates risk factors of age and health status by incorporating coefficients into parameters of F, β, and ω. Experimental results show the capability of the SPA to demonstrate the effectiveness of adopting a healthier lifestyle and of self-awareness in a quantitative way. Due to the self-awareness, the SPA had a better control of BG levels than the CPA. These results showed the importance of SMBG and self-awareness.

Another important area of research is to judge several levels of blood glucose monitoring frequency. The motivation for this research is that SMBG is highly recommended for people with Type 2 diabetes; however, a high intensity of monitoring leads to discomfort, potential infection and a financial burden, so it is increasingly necessary to investigate optimal frequencies in order to reduce these inconveniences. The conventional method of RCT *in vivo* has obvious disadvantages such as it being time consuming, the huge cost associated with it and inherent difficulties in studying rare events. Our method of calculating NCCZLs and AVDs and observing their mean and variance to examine the frequency *in silico* is, by comparison, far preferable. The BG data is generated by the SPA model. NCCZLs illustrate the similarity between the interpolation and the CBG, and AVDs show their deviation, a combination of which can adequately demonstrate how well the samples can represent the CBG. To investigate a

personalized optimal MF, the SPA is categorized into nine groups in terms of age and health status. A number of experiments are conducted to simulate the nine categories with different MFs. An evaluation table is created in order to present optimal MF for each SPA.

After evaluating the efficiency of various lifestyles, the self-awareness and the treatment through SMBG in a micro scope of the CPA and SPA models, we further propose a multi-agent system by introducing other healthcare components in order to observe other factors such as the healthcare quality, cost and performance in a macro scope. However, we only present a design of the multi-agent system so far. Further experiments will be conducted in the future.

In the proposed ABS simulation models, several cost-effective experiments in different simulation scenarios are implemented *in silico*, as it is often not possible or too difficult, dangerous or unethical to do them *in vivo*. By analyzing the simulation results, we intend to build a base line of treatment strategies *in silico* rather than construct a guideline for a specific individual *in vivo*. However, this research may assist human patients to determine a personalized management regimen based on their unique situation.

Additionally, we are trying to develop a framework of a simulation healthcare system rather than in-depth research on a specific disease. Existing models, such as the Ackerman model, are integrated into the software agent to reduce the risk and time associated with exploring a mathematical model ourselves. Since existing models are not tailored for our research, complimentary models, such as the RW model, are also developed. These concepts make it possible to change or add mathematical models for other purposes. For instance, concerning other risk factors such as blood pressure and

obesity can make the tool more useful and practical. This system can even be transferred to simulate other diseases by changing mathematical models.

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