UNIVERSITY OF SOUTHERN QUEENSLAND

DEPTH OF ANAESTHESIA CONTROL TECHNIQUES AND HUMAN BODY MODELS

A Dissertation submitted by

Shahab Anna Abdulla

For the award of

Doctor of Philosophy

2012

To my family

Abstract

The objective of this project is to develop patient dose-response models and to provide an adequate drug administration regimen for anaesthesia to avoid under- or over-dosing of patients. The controllers are designed to compensate for patients' inherent drug response variability, to achieve the best output disturbance rejection, and to maintain optimal set point response.

To address this issue, this project uses four independent methods to investigate the control strategies for the regulation of hypnosis. Two medications are used in a thorough evaluation and comparison of controller performance.

A robust internal model controller (RIMC) based on the Bispectral Index (BIS) is investigated firstly. The controller compares the measured BIS with its input reference to provide the expected Propofol concentration, and then the controller manipulates the anaesthetic Propofol concentration entering the anaesthetic system to achieve the desired BIS value. This study also develops patient dose-response models. The performance of the RIMC is comprehensively compared with that of proportional-integral-derivative (PID) controller for the robustness, set-point changes, disturbances and noise in the measured BIS. Numerical simulations illustrate that the RIMC performed better than the PID controller. The robust performance of the two controllers is evaluated for a wide range of patient models by varying in patient parameters.

The impact of the time-delays of patient and instrumentation on a closed-loop depth of anaesthesia control system was investigated. In this study, the Smith predictive

technique is used to identify and compensate for the time-delay problem and improve the overall response of the depth of anaesthesia. The proposed method is validated using measured BIS signals in simulation. The results showed that the proposed procedure improves the performance of the closed-loop system for reference tracking and overall stability. The proposed method also has approximately 15% less overshoot, a two minute shorter settling time, and is more robust to disturbance rejection.

The problem of non-linearity is identified in the depth of anaesthesia model and a deadbeat controller is designed in response to this problem. The proposed system is evaluated in simulation using Matlab and Simulink, and results are compared with a traditional PID control system and with an internal model control (IMC) controller. The results show that the proposed scheme has less over- and under-shoot, shorter settling time and is more robust to depth of anaesthesia disturbances. In addition, the proposed method is easy to implement.

The Model Predictive Control (MPC) technique is also investigated in depth of Anaesthesia (DoA) control. The proposed robust control system with a predictive controller is evaluated in simulation. The result is compared with two control systems. First compared with a conventional PID controller and then with a control system with an Internal Model Controller. The results show that the proposed scheme has a smaller overshoot (by about 10%) and a shorter settling time (by about 2 minutes shorter) and is more robust to disturbances caused by parameter changes.

Certification of Dissertation

I certify that the ideas, experimental work, results and analyses, software and conclusions reported in this dissertation are entirely my own effort, except where otherwise acknowledged. I also certify that the works is original and has not been previously submitted for any other award, except where otherwise acknowledged.

_____ _____

Shahab Anna Abdulla, Candidate Date

ENDORSEMENT

_____ _____

A/ Prof. Peng (Paul) Wen, Principle supervisor Date

_____ _____

Dr. Wei Xiang, Associate supervisor Date

Acknowledgements

I am highly grateful to my thesis advisors, Associate Professor Peng Wen for his endless commitment to directing research, and my appreciation to him for his insightful remarks, valuable comments and ideas for all these years. He has provided me excellent guidance to work enthusiastically and develop critical thinking abilities. I am extremely thankful to him for his invaluable suggestions and constant encouragement. He taught me many other things apart from technical matters, which will definitely assist me in achieving my future livelihood goals.

I would like to express my gratitude to A/Prof Yan Li for her, support, motivation, encouragement, advice, comments and discussions.

I am thankful to the Ministry of Higher Education and Scientific Research of Iraq who gave the opportunity to do my Ph.D. study at the USQ. In addition, a special thanks to my friends and colleagues at USQ especially Richard Landers and Salman Shahid for their support and encouragement.

I am tremendously thankful and grateful to my beloved wife Zainab who always encouraged and supported me with her deepest love and affection all these days.
I would like thank my mother, sisters and brothers for their everlasting affection, love and constant support throughout my life.

Related Publications

During Dissertation Period

Abdulla, SA & Wen, P, 2011, "Robust internal model control for depth of anaesthesia," International Journal of Mechatronics and Automation, vol. 1, pp. 1-8, 2011.

Abdulla, SA & Wen, P, 2011, "Depth of anaesthesia patient models and control," in Complex Medical Engineering (CME), 2011 IEEE/ICME International Conference on, 2011, pp. 37-41.

Abdulla, SA & Wen, P, and Xiang, W, 2010, "The design and investigation of model based internal model control for the regulation of hypnosis," in Nano/Molecular Medicine and Engineering (NANOMED), 2010 IEEE 4th International Conference on, 2010, pp. 192-197.

Abdulla, SA & Wen, P 2010, "Depth of anesthesia control using internal model control techniques," presented at the 2010 IEEE/ICME International Conference on Complex Medical Engineering (CME2010), Gold Coast, Australia, 2010.

Abdulla, SA & Wen, P 2012, "The effects of time-delay on feedback control of depth of anesthesia," presented at the 2012 IEEE-EMBS International Conference on Biomedical and Health Informatics (BHI 2012), Hong Kong, Shenzhen, China, 2012.

Abdulla, SA & Wen, P 2012, "Depth of Anaesthesia Control Investigation Using Robust Deadbeat Control Technique," International Conference on Complex Medical Engineering (CME 2012), Kobe, Japan, 1-4 July, 2012.

Table of Contents

Abstract……. ii

Certification of Dissertation……... iv

Acknowledgments……..…… ..…. v

Related Publications during DissertationPeriod……..…….…….…….…. vi

Table of Contents…….…….…… vii

List of Abbreviations……..……..……..... x

List of Symbols… ……..…… xii

List of Tables……..……..……..……..…….…….xiii

List of Figures…..……..…….…….. … xiv

CHAPTER 1 1

INTRODUCTION..... 1

1.1 ANAESTHESIA AND REGULATION IN OPERATION THEATRES 1
1.2 DEPTH OF ANAESTHESIA CONTROL AND MONITORING 4
1.3 PATIENT MODEL AND HYPOTHESES FOR DOA CONTROL 7
1.4 RESEARCH OBJECTIVES 12
1.5 STRUCTURE OF DISSERTATION 14

CHAPTER 2 18

LITERATURE REVIEW..... 18

2.1 BACKGROUND 18
2.2 FEEDBACK CONTROL OF ANAESTHESIA..... 19
2.3 PATIENT BODY DYNAMICS AND MODELS 23
2.3.1 Body and interaction to anaesthetic medicine..... 23
2.3.2 Patient body kinetics 24

2.3.3 Patient body dynamics *26*
2.3.4 Models for control *26*
2.4 CONTROL TECHNIQUES FOR DOA 27
2.4.1 Model based predictive control in DoA *28*
2.4.2 Time-delay in DoA control *30*
2.4.3 Deadbeat control in DoA *32*
2.5 SUMMARY 34

CHAPTER 3 35

HUMAN BODY AND MODELS 35

3.1 KINETICS AND DYNAMICS OF HUMAN BODY 35
3.2 PHARMACOKINETIC MODEL 37
3.3 PHARMACODYNAMIC MODEL 40
3.4 TIME-DELAY IN RESPONSE 41
3.5 INTRA-PATIENT UNCERTAINTY 42
3.6 INTER-PATIENT UNCERTAINTY 46
3.7 SUMMARY 50

CHAPTER 4 51

DOA INTERNAL MODEL CONTROL USING SIMPLIFIED PATIENT MODEL 51

4.1 INTERNAL MODEL CONTROL TECHNIQUE 51
4.2 PATIENT MODEL FOR IMC CONTROL 53
4.3 CONTROLLER DESIGN AND IMPLEMENTATION 56
4.4 SIMULATION AND RESULTS 60
4.5 CONCLUSIONS 72

CHAPTER 5 73

SMITH PREDICTIVE CONTROL FOR PATIENT MODEL WITH TIME-DELAY 73

5.1 HUMAN BODY MODEL FOR DEPTH OF ANAESTHESIA CONTROL 73
5.1.1 Time-Delay estimation *78*
5.1.2 Identifying the PK time-delay *82*
5.2 SMITH PREDICTOR AND CONTROLLER DESIGN 83
5.3 PERFORMANCE EVALUATION IN SIMULATION 87
5.4 CONCLUSIONS 92

CHAPTER 6 94

ROBUST DEADBEAT CONTROL FOR PATIENT MODEL WITH UNCERTAINTIES 94

6.1 UNCERTAINTIES AND DISTURBANCES IN DOA CONTROL 94
6.2 PATIENT MODEL WITH UNCERTAINTIES 95
6.3 ROBUST DEADBEAT CONTROL (RDC) TECHNIQUE 101
6.4 APPLICATIONS OF RDC TO DOA CONTROL 104
6.5 SIMULATION AND RESULTS 106
6.6 CONCLUSIONS 111

CHAPTER 7 112

MODEL PREDICTIVE CONTROL OF DOA 112

7.1 MODEL PREDICTIVE CONTROL TECHNIQUE 112
7.2 MODEL PREDICTIVE CONTROL DESIGN 117
7.2.1 Constraints 120
7.2.2 Time horizons 121
7.2.3 The simulation model of MPC 122
7.3 RESULTS AND DISCUSSION 123
7.4 CONCLUSIONS 134

CHAPTER 8 135

CONCLUSIONS AND FUTURE WORK 135

8.1 REVIEW OF RESEARCH 135
8.2 GENERAL CONCLUSIONS 136
8.3 FUTURE WORK 139

REFERENCES 141

List of Abbreviations

AEP	Auditory Evoked Potential
ASA	American Society of Anaesthesiologists
BIS	Bispectral Index
CEPOD	Confidential Enquiry into Postoperative Deaths
CMEC	Cascade control with Modeling Error Compensation
CO	Cardiac Output
Cp Alf	Plasma Alfentanil Concentration
CV	Controlled Variable
DoA	Depth of Anaesthesia
EEG	Electroencephalogram
EMG	Electromyogram
FMA	Fuzzy Modelling Algorithm
GFLC	Genetic Fuzzy Logic Controller
GPIDC	Genetic Proportional Integral Derivative Controller
HR	Heart Rate
ICU	Intensive Care Unit
IMC	Internal Model Control
LOC	Loss of Consciousness
LTI	Linear Time Invariant
MAP	Mean Arterial Pressure
MBPC	Model Base Predictive Control
MEC	Modeling Error Compensation Control

MIMO	Multiple Input-Multiple Output
MPC	Model Predictive Control
NCS	Networked control systems
NMB	Neuromuscular Block
NONMEM	NON linear Mixed Effect Models
PD	Pharmacodynamics
PI	Proportional-Integral Control
PID	Proportional-Integral-Derivative Control
PK	Pharmacokinetics
PKPD	Pharmacokinetic - Pharmacodynamic
PWM	Pulse Width Modulator
RIMC	Robust Internal Model Control
SAP	Systolic Arterial Pressure
SISO	Single Input-Single Output
SOFLC	Self-Organizing Fuzzy Logic Control
SP	Smith Predictor
SPC	Smith Predictor Control
TCI	Target-Controlled Infusion

List of Symbols

C_{50}	drug concentration at 50% of maximal effect
C_e	concentration of drug at the effect-site (propofol-µg/ml, Remifentanil-ng/ml)
E_{max}	denotes the maximum effect achieved by the anaesthetic infusion
k_{10}	elimination rate constant (min^{-1})
k_{12}, k_{21}, k_{13} & k_{31},	drug transfer rates between the peripheral and central compartments (min^{-1})
k_{e0}	equilibration constant for the effect-site (min^{-1})
γ	degree of nonlinearity (dimensionless)
E	the effect-site compartment
V_1	volume of the central compartment (l)
V_j (j = 2, 3)	volume of the auxiliary compartments (l)
EC_{50}	concentration of drug at half-maximal effect (vol.%)
k_{ij}	drug transfer rate constants between auxiliary and central compartments (min^{-1})
u	drug infusion rate with respect to patient weight (propofol - mg/kg/hr, remifentanil - µg/kg/min)

List of Tables

Table 1.1	Incidence of awareness during surgery	2
Table 1.2	Contemporary anaesthetic mortality rates	3
Table 1.3	BIS values and associated hypnotic states	6
Table 3.1	Pharmacokinetic parameter values	39
Table 3.2	Parameter estimaes from the NONMEM analysis	45
Table 3.3	Propofol PK parameter sets	46
Table 3.4a	PD models	47
Table 3.4b	PD models	48
Table 3.5	Propofol PK-PD Inter-patient variability	48
Table 3.6	Intra- and Inter-patient Variability	49
Table 4.1	Values of the parameters for the 15 patients Sets arranged in the decreasing order of their BIS sensitivity to Propofol infusion	63
Table 5.1	Values of the parameters for the 12 patients sets arranged in the decreasing order of their BIS sensitivity to propofol infusion	79
Table 6.1	Deadbeat coefficients and response times	102
Table 7.1	Model predictive controller constraints	121
Table 7.2	Nominal patient’s data for DoA parameters	126
Table 7.3	Patient PK-PD parameters for propofol drug used in this study	128
Table 7.4	Patient PK-PD parameters for remifentanil drug used in this study	129

List of Figures

Figure 1.1	Bispectral Index Scale and its meaning	7
Figure 1.2	Pharmacokinetic-pharmacodynamic models	9
Figure 1.3	Effect-site concentrations (ng/ml)	10
Figure 3.1	Human body modeling	37
Figure 3.2	Bolus vs infusion pharmacokinetic of propofol	43
Figure 4.1	Depth of anaesthesia model for internal model control	53
Figure 4.2	Pharmacokinetic compartments model	54
Figure 4.3	Block diagram of the Internal Model Control	57
Figure 4.4	Block diagram of the IMC structure	60
Figure 4.5	The block diagram of DoA model built in Simulink Simulink	61
Figure 4.6	Non-linear DoA model built in Simulink	62
Figure 4.7	Performance of the IMC controller	65
Figure 4.8	Performance of the PID controller	66
Figure 4.9	Performance of the IMC for two insensitive patients	67
Figure 4.10	Performance of the IMC for different patients	67
Figure 4.11	Performance of the PID for different patients	68
Figure 4.12	Performance of the PID for two insensitive patients	69
Figure 4.13	Parameters influence on the DoA and on k_{e0}	70
Figure 4.14	Performance of the IMC and PID controller	70
Figure 4.15	Performance of the IMC and PID controller	71
Figure 5.1	Depth of anaesthesia model for Smith predictive control	77

Figure 5.2	Feedback control system for SPC	78
Figure 5.3	The representation of the real and simulated BIS	80
Figure 5.4	The block diagram of Smith predictive control	84
Figure 5.5	The control system structure with the Smith predictor	85
Figure 5.6	The equivalent block diagram by applying the Smith predictor	86
Figure 5.7	Smith predictor with nominated time-delay	88
Figure 5.8	Smith predictor without time-delay	89
Figure 5.9	Smith predictor with time-delay for three different patients	90
Figure 5.10	Smith predictor with time-delay for two different patients	90
Figure 5.11	Smith predictive control simulation's block diagram	91
Figure 5.12	Performance of SPC for different patients	91
Figure 5.13	SPC for three different patients	92
Figure 6.1	The pharmacokinetic model	96
Figure 6.2	The pharmacodynamic model	100
Figure 6.3	Robust deadbeat control structures	102
Figure 6.4	Robust deadbeat control structure for DoA	104
Figure 6.5	Implementation of a robust deadbeat control structure for DoA	106
Figure 6.6	DoA robust deadbeat control response	107
Figure 6.7	DoA robust deadbeat control response for different values of K	107
Figure 6.8	Comparison of the performance of the Deadbeat with, IMC and PID controllers'	108
Figure 6.9	DoA deadbeat control response for different patients	109
Figure 6.10	DoA deadbeat control response for changing patient's parameters	110
Figure 7.1	Compartmental model of the patient	115
Figure 7.2	Model predictive control scheme	117

Figure 7.3 The basic concept of model predictive control 118
Figure 7.4 The model predictive control simulation design 123
Figure 7.5 The performance of the MPC for nominal patient 124
Figure 7.6 MPC controller performance for different R, and Q weights 125
Figure 7.7 The performance of MPC, IMC and PID controllers for sensitive Patient 127
Figure 7.8 The performance of MPC controllers for four insensitive patients 130
Figure 7.9 The performance of MPC controllers for sensitive patient number 2 131
Figure 7.10 The performance of MPC controllers for sensitive patient number 4 131
Figure 7.11 The Simulink model structure 132
Figure 7.12 The performance of MPC controllers for sensitive patient number 3 133
Figure 7.13 The performance of MPC controllers for sensitive patient number 3 133

CHAPTER 1

INTRODUCTION

1.1 Anaesthesia and Regulation in Operation Theatres

During surgery general anaesthesia renders a patient unconscious and without pain or memory. Anaesthesia professionals may use three medications: hypnotic drugs to numb the brain so the patient will be asleep and will not remember the surgery, analgesic drugs to prevent pain, and paralytics to keep the patient still when surgeon is working. Knowing the exact amount of each medication a patient requires present a great challenge because each person has individual needs and these needs change during surgery. If too little hypnotic is given, the patient is at risk of anaesthesia awareness or unexpected awaking. If too little analgesic is given, the patient may also experience pain during surgery. Some of these patients will be aware and feel pain but be unable to move or speak. More commonly, too much anaesthesia may be given which can prolong the waking period or increase other side effects. Table 1.1 shows the incidence of awareness. In other words, there are still a large number of patients who remain awake during surgery due to lack of anaesthetise (Bruhn et al. 2006).

Table 1.1: Incidence of awareness during surgery (Bruhn et al. 2006).

Author	Year	Sample	Awareness
Hutchinson	1960	656	1.2
Harris	1971	120	1.6
McKenna	1973	200	1.5
Wilson	1975	490	0.8
Liu et al	1990	1000	0.2
Sandin	1997-1998	11785	0.15
Myles	1993-2000	10811	0.11
Sebel	2001-2002	19575	0.13
Ekman et al	2003	7826	0.18
Lennmarken& Sandin	2004	1238	0.9
Rungreungvanick	2005	150000	0.07

Brain monitors, such as the Bispectral Index monitor, can now be used to measure a patient's brain response to anaesthesia. This information helps clinicians to adjust the amount of medication to improve recovery from anaesthesia; and it also helps clinicians to reduce the risk of patient awareness (Downey & Seagrave 2000; Foster, Bojak & Liley 2008; Furutani et al. 2010; Gaohua, Maekawa & Kimura 2006; Glass et al. 1997).

Currently, anaesthesia is one of the safest components of any operations. In 1986, a survey (Spence 1988) revealed that the overall death rate attributable directly to anaesthetic medications was 1:185,056, as shown in Table 1.2 (Brown 1992). Of the approximately 28 million patients undergoing anaesthesia and surgery in the United

States, it is estimated that about 150 patients die each year from difficulties and complications due to anaesthesia (Wiklund & Rosenbaum 1997).

Table 1.2: Contemporary anaesthetic mortality rates adapted from (Brown 1992)

Study	Year	Total Cases	Mortality Rate
Beecher	1948-1952	599,548	1:1,560 [a]
Clifton	1952-1962	205,640	1:3,955 [a]
Harrison	1967-1976	240,483	1:4,537 [b]
Hatton	1977	190,380	1:2,885 [a]
Lunn	1979	1,147,362	1:6,789 [e]
Eichhorn	1976-1985	757,000	1:151,400 [d]
Eichhorn	1985-1988	244,000	0 [d]
CEPOD	1986	486,000	1:185,056 [e]
CEPOD	1986	486,000	1:185 [c]

a: All operation cases considered in calculation
b: Cases included if death occurred in less than 24 hours
c: Cases included if some contribution by anaesthetic
d: Only ASA physical status I and II patients included
e: Only deaths directly attributable to anaesthetic included
CEPOD: Confidential Enquiry into Postoperative Deaths

Depth of anaesthesia (DoA) can be defined as the lack of response and recall to noxious stimuli. The anaesthetic management of a surgical patient is a process that relies on the experience of an anaesthetist as there are currently no direct means of assessing a patient's level of consciousness during surgery. The decision for the initial anaesthetic level is generally made using the recommended drug dosages based on different patient characteristics, such as age and weight (Lemos et al. 2006). The anaesthetist determines any subsequent alteration in the anaesthetic level by observing physical signs from the patient (McAnulty, Robertshaw & Hall 2000). These physical signs, the indirect indicators of the depth of anaesthesia, may include

changes in blood pressures or heart rate, lacrimation (the production of tears in the eyes), facial grimacing, muscular movements, spontaneous breathing, diaphoresis (sweating, especially sweating induced for medical reasons), and other signs that may predicate awareness.

However, they are not reliable indicators of changes in patients' levels of consciousness. Although an anaesthetist can adjust recommended anaesthetic dosages based on individual patient characteristics, these adjustments cannot always account for variability in patient responses to anaesthesia or changes in anaesthetic requirements during the course of surgery (Bruhn 1999).

Anaesthetic under-dosing can cause intra-operative awareness, and explicit cognizance, resulting in postoperative psychological consequences. The need for a reliable technique for controlling the anaesthetic titration has prompted anaesthetists to overdose in order to prevent possible intra-operative awareness. However, anaesthetic overdosing prolongs the recovery period, which increases healthcare costs and the utilization of post-recovery care.

1.2 Depth of Anaesthesia Control and Monitoring

The major difficulty in the design of automatic controllers for anaesthesia is the inherent patient variability due to differences in demographics and drug tolerance (Saldien, Vermeyen & Wuyts 2003). These discrepancies have been translated into the pharmacokinetics-pharmacodynamics (PKPDs) dose-response model uncertainty that may affect the stability of the closed loop system. A controller is considered to be robust if it is insensitive to the differences between the actual patient's drug-

response and the nominal model for which the controller was designed (Dumont, Martinez & Ansermino 2009).

The potent agents used in the practice of anaesthesia have narrow therapeutic margins, so accurate control of anaesthesia is of utmost importance. The significance of a robust controller is to provide an adequate drug administration regimen for the anaesthesia to avoid the under-or over-dosing of patients. The controller is designed to compensate for patients' inherent drug response variability, to achieve better disturbance rejection, and to attain good set point response.

In the past, anaesthetists relied solely on clinical signs to assess the depth of anaesthesia because of the lack of a single widely accepted indicator for anaesthetic adequacy. Nowadays there are a number of monitoring tools available to quantify the EEG, in order to derive a surrogate measurement of hypnosis (Kissin 2000).

Snow (1847) first used clinical signs such as breathing patterns, eyeball movements and the inhibition of intercostal muscles to describe five degrees of narcotism for ether anaesthesia. Guedel (1920) discovered four stages of ether by using somatic muscle tone, respiratory patterns and ocular signs. These methods have been proven not to provide a dependable guide for depth of anaesthesia assessment while using multiple types of anaesthetics. Heart rate (HR), and mean arterial pressure (MAP), are also regularly used to monitor patient status. Ghouri et al. showed that hemodynamic responses (HR and MAP) could be attributed to several factors (Ghouri, Monk & White 1993). However, measurements of these quantities do not

give a satisfactory indication of the level of drugs required, and further indicators must be considered.

More recently, Bispectral Index (BIS) monitoring systems have been gaining clinical approval as a strong indicator of anaesthetic depth with respect to a variety of anaesthetics (Rosow & Manberg 2001). In general, BIS monitor allows anaesthesia professionals to access processed EEG information (Kreuer et al. 2001) as a measure of the effect of certain anaesthetics on patients (Glass et al. 1997). The clinical impact of BIS monitoring has been demonstrated in a variety of randomized controlled trials, these trials have revealed the potential for BIS monitoring to facilitate improvements in patient safety during anaesthesia care (Struys et al. 2004; Struys et al. 2003). The range of BIS values are stated in Table.1.3 (Drummond 2000).

Table 1.3: BIS values and associated hypnotic states (Drummond 2000).

BIS value	Hypnotic state
0	Depressed EEG
20	Profound anaesthetic level
40	Deep hypnotic level
60	Moderate hypnotic level
80	Sedated
100	Awake

The BIS is scaled between 0 and 100. A value of 100 represents the conscious state. With increasing concentration of anaesthetics, the index decreases (Hui-Hing, Beck & Bloom 2004). During general anaesthesia the index sits between 60 and 40, as

shown in Figure 1.1. Lower values represent deep hypnotic states, while values between 90 and 60 usually represent sedation levels (Bibian 2006).

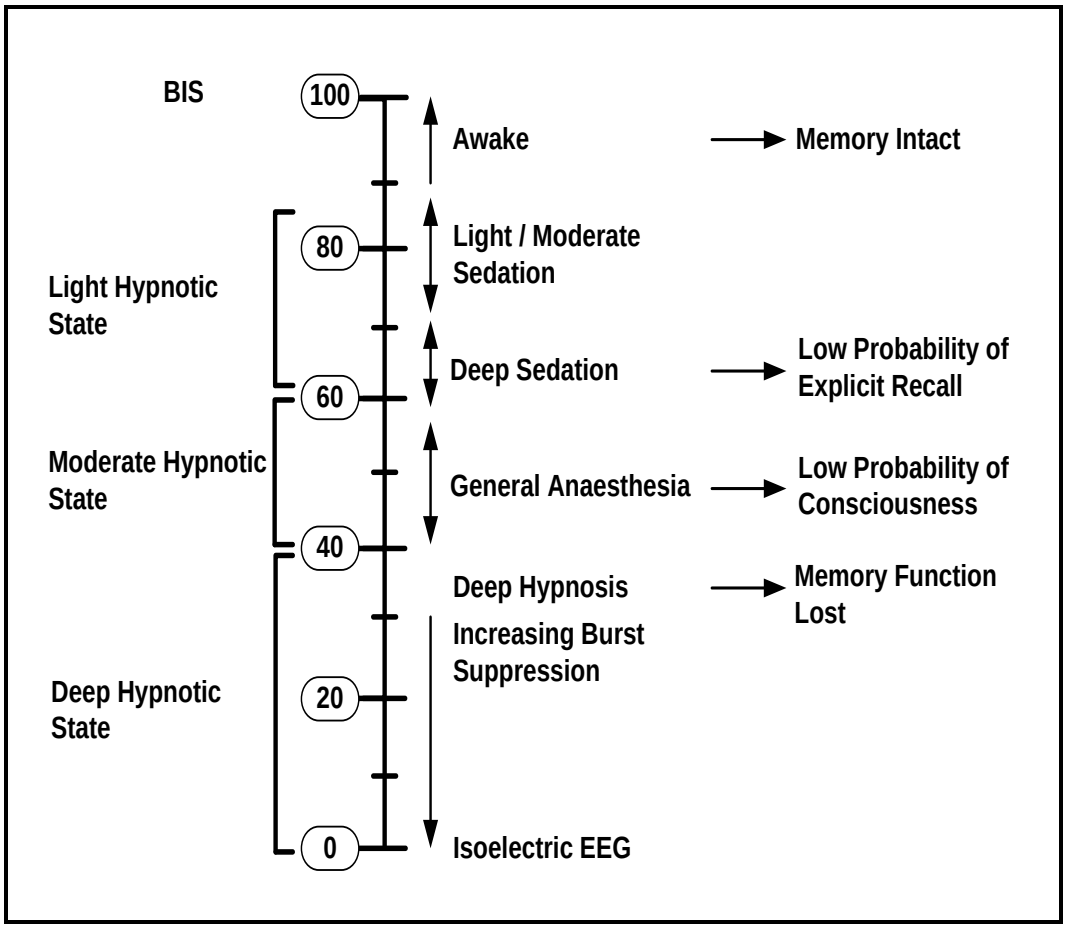

Figure 1.1: Bispectral Index Scale and its meaning (Zikov et al. 2002)

1.3 Patient Model and Hypotheses for DoA Control

The design of a robust controller for automating anaesthesia requires a reliable mathematical model to represent anaesthesia (hypnotic, paralytic and analgesic) dynamics, as well appropriate hardware devices to calculate and monitor the depth of anaesthesia. The mathematical model should precisely represents the relationship between the administered anaesthetic amount and its effect on the patient in terms of

hypnosis, paralysis and analgesia (Yelneedi, Samavedham & Rangaiah 2009). Pharmacokinetic (PK) and pharmacodynamic (PD) modeling is the route of constructing mathematical model for the time course of dose to concentration (pharmacokinetics) and concentration to effect (pharmacodynamics) (Minto, & Schnider, 2008). Intravenous anaesthesia is concerned with the use of intravenous drugs to attain the desired effects throughout the induction of anaesthesia during surgery, and in the early postoperative period (Masui et al. 2009). The major medication classes used for enhancing general anaesthesia during surgery are the hypnotics, the analgesics, and the paralytics (Homer & Stanski 1985). These have given a guarantee of unconsciousness and the smooth progress of endotracheal intubation, which provides analgesia, and suppresses the hemodynamic and neuroendocrine responses to surgery (Homer & Stanski 1985; Manyam et al. 2006; Minto et al. 1997; Muñoz et al. 2004).

The main objectives are that the patient should speedily lose consciousness and experience no consciousness during the operation. The level of analgesia should closely follow the level of surgical stimulation to ensure hemo-dynamic stability; the medication effects should rapidly wear off at the end of the surgery so that the patient has no residual sedation, no residual muscle paralysis, and, ideally, no respiratory depression and no painful sensation from the surgery of trauma (Vanluchene et al. 2004).

This study of pharmacokinetics is particularly interested in compartmental (three-compartment models), the effect-site concept (characterized by the rate constant

k_{e0}), and the Hill equation (which defines the concentration–effect relationship) as shown in Figure 1.2 and Figure1.3 (Bailey & Haddad 2005).

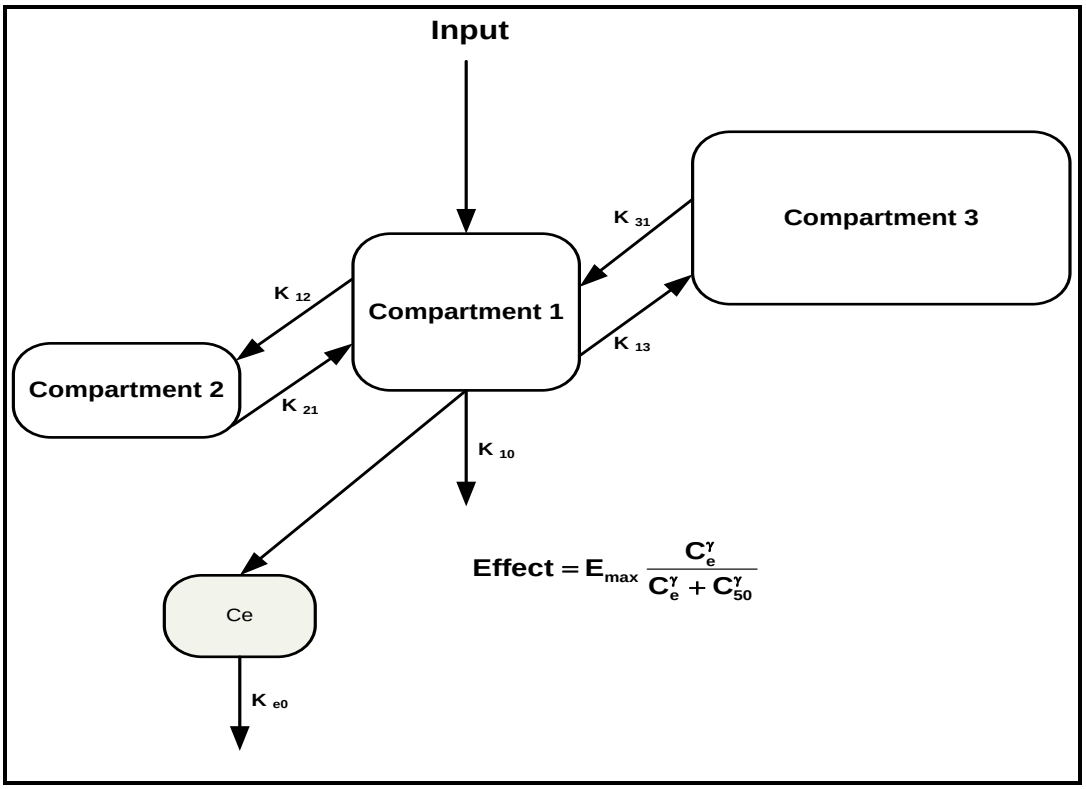

Figure 1.2: Pharmacokinetic-pharmacodynamic models

In contrast to anaesthesia, which involves the administration of most of the medications by intravenous bolus or infusion for procedures lasting minutes to hours, many other specialties involve the administration of drugs by repeated oral dosing for conditions lasting weeks, months, or years. Anaesthesia relies increasingly on drugs with a very rapid onset of effect (1–2 min), whereas in some medical specialties the onset time is measured in weeks (Minto, & Schnider, 2008; Mourisse et al. 2007; Munson & Bowers 1967; Nunes, & Mendonça 2005). As a result, many pharmacokinetics and pharmacodynamics studies make up the anaesthesia literature.

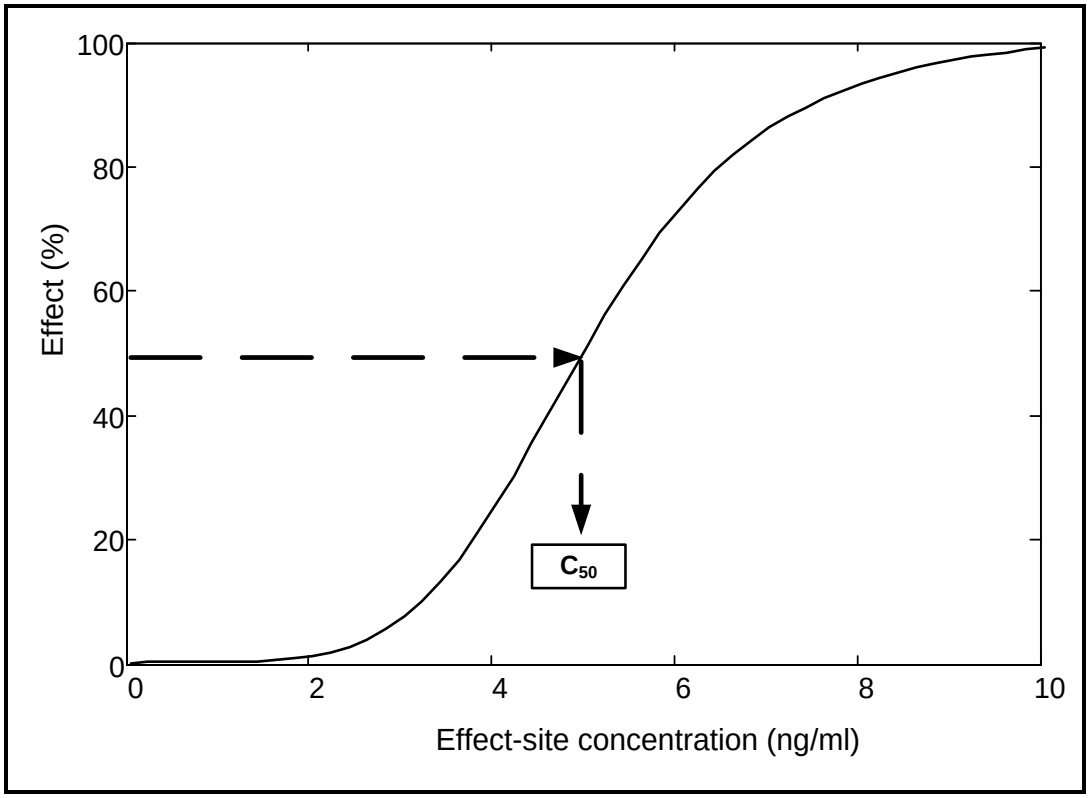

Figure 1.3: Effect-site concentrations (ng/ml)

A combination of anaesthetics, with or without neuro-muscular blocking (NMB), are administered together to create the state of general anaesthesia. These medications, even, when taken within the same family, have different properties. Since they provide the actuators through which the patient's state can be regulated (i.e., allowing the control of the anaesthetic state), it is necessary to provide control engineers with some knowledge of the mechanisms of action of the most commonly used drugs (Bibian 2006).

Inhaled anaesthetics: With the advent of fluorine technology in the 1940s, new inhaled anaesthetics were developed. Compared to ether and chloroform, fluorine compounds have lower blood solubility (thus ensuing rapid induction and recovery), lower toxicity, are less irritating to the airway, and are not flammable. Nowadays

three agents are commonly used with or without nitrous oxide: isoflurane, desflurane and sevoflurane. All these agents provoke a decrease in mean arterial blood pressure when administered to healthy subjects.

Intravenous anaesthetics: Intravenous anaesthetics can be classified into five families: Barbiturates (thiopental), Benzodiazepines (midazolam, diazepam, lorazepam), Phencyclidines (ketamine), Carboxylated imidazoles (etomidate), and Isopropylphenols (propofol). Compared with volatile agents, intravenous anesthetics (besides ketamine) do not provide analgesic effects-hence, they are defined as hypnotic rather than anaesthetic drugs. However, opioids and intravenous anaesthetics, when used in combination, are strongly synergistic both in terms of hypnosis and in terms of analgesia. Propofol has introduced in the early 1990s and has become the intravenous drug of choice in anaesthesia. Two particular characteristics of propofol are its fast redistribution and its metabolism. As a result it can be easily used in infusion schemes as it provides very fast emergence, without cumulative effect.

Neuromuscular blockade (NMB): NMB medication blocks the transmission of nerve impulses at the neuromuscular connection, and paralysis the skeletal muscles. Mechanical ventilation should be given to maintain sufficient respiration, because NMB also paralysis the muscles required for breathing. These treatments are used together with hypnotics and/or analgesics to create skeletal muscle relaxation and facilitate intubation of the trachea and to give optimal surgical conditions. May sometimes NMB causes transient hypotension but does not have any hypnotic or analgesic properties. In addition, these do not work together, in a clinically significant way, with anaesthetics and opioids. When a longer effect is required NMB types such as Vecuronium, Mivacurium and Rocuronium are normally used

(Sreenivas, Lakshminarayanan & Rangaiah 2007). With the introduction of NMB medications in the early 1940, the risk of incomplete paralusis vanished. A growing number of intra-operative cases related to the use of NMB were reported.

The hypotheses to be addressed in this PhD thesis are:

1. Robust model based predictive control strategies can be developed to control nonlinear systems with input and state constraints to give nearest time optimal control.
2. These strategies will give improved or better performance than the existing strategies that consider input and state constraints.
3. Set point changes are often made during the surgical procedure. The controller should completely respond to these changes without any delay. In addition, disturbances occur during the operation depending on the strength of the surgical stimulus. The designed controller should guarantee the required anesthetic depth in the patient in spite of these disturbances.
4. Drug delivery constraints and the maximum amount of drug infused are most important for patient safety and these constraints should be explicitly included in the designed closed-loop feedback controller algorithm.

1.4 Research Objectives

The aim of this dissertation is to construct and develop accurate feedback control of DoA, and a reliable mathematical model for model base predictive control of DoA. The research also compares performance of MBPC strategies with conventional control methods such as PID controllers for DoA. It also analyses and develops the

strategies to ensure the robustness and stability of the system in the presence of nonlinearities such as parameter variations, disturbance rejection, noise suppression etc.

The mathematical model employed in recent studies on depth of anaesthesia control is a series combination of a linear PK model and a nonlinear PD model. A theoretical effect compartment is also attached to the central compartment to represent the time-lag between observed effect and central (plasma) concentration. The parameters used in the PK and PD models are the population mean values and the "patients" would have parameters that are different from the nominal values used in the controller design. The PK model parameters can be estimated approximately through covariate adjustments of weight, age, and sex, but it is impossible to estimate the PD parameters. Therefore, the designed controller should be robust and result in stable responses for all patients characterized by a range of PD parameters.

The following specific objectives are formulated to achieve the research aim. The objectives are to apply and evaluate the promising MBPC and IMC approaches for DoA regulation using the Bispectral Index as the controlled variable, to manipulate propofol (a new intravenous anaesthetic) infusion and also to verify DoA models via simulation and model validation methods.

This research will result in the publications of predictive control algorithms for nonlinear systems with input and state constraints. These algorithms will deliver a performance superior to any other contemporary control algorithms. The stability and robustness analysis will ensure that the system stays stable and can withstand

parameter variations and disturbances. The new control methods can be used to control multivariable structures and will be very useful in the control of nonlinear systems, in particular DoA.

An automatic controller that infuses drugs based on the patient's anaesthetic level will provide the following benefits:

1. It will reduce the anaesthetist's workload during the surgery and allow him/her to monitor and deal with other critical aspects of the surgery (blood loss, sudden blood pressure change, etc.).
2. Better depth of anaesthesia will be achieved compared to manual administration because the controller variable is sampled more frequently leading to active adjustment of the delivery rate of the drug.
3. A well-designed automatic control system can tailor the drug dosage based on the patient's response, which avoids both over-dosage and under-dosage of the drugs. Overall, these improve the patient's rehabilitation and safety during and after the surgery.

1.5 Structure of Dissertation

This dissertation contains eight chapters addressing the importance of the processes involved in depth of anaesthesia control and a detailed description of the scope of the present work. The structure of the dissertation is given below:

Chapter 1 introduces the objectives of the dissertation and gives an introduction of the features of depth of anaesthesia, input, controller, modelling, and output. This

chapter introduces anaesthesia regulation, and then mathematical model structure, anaesthetics, depth of anaesthesia monitoring, research hypotheses. A short discussion of depth of anaesthesia is presented to give the reader with basic background material.

Chapter 2 presents an extensive review of the various control strategies applied in clinical anaesthesia. This chapter also provides a complete overview of the modeling that is generally used in anaesthesia. In addition, some detailed control techniques for depth of anaesthesia is introduced.

Chapter 3 focuses on human body mathematical models and the medication delivery system. This chapter provides the effect of the time dealy on depth of anaesthesia response. It also describes intra and inter-patient uncertainties in human body model.

Chapter 4 investigates the internal model control technique in DoA. The first part focuses on the theoretical concepts of the depth of anaesthesia model and describes the internal model control. The second part of this chapter details the experimental and simulation work and discusses the results. This chapter covered three main elements:

1. The theoretical considerations are used to give a fundamental understanding of the patient mathematical model of depth of anaesthesia.
2. The experimental and simulation work includes a detailed explanation of the internal model control in Matlab and Simulink.

3. The last part of this chapter analyses the simulation results and compares the results with the performances of a PID controller.

Chapter 5 addresses a closed-loop depth of anaesthesia control system, which applies Smith Predictive Technique to identify and compensate the problem caused by time-delay. This chapter also includes the description of a human body model used in this study. This chapter coveres three main elements:

1. The overall time-delay can be considered into two parts. The first is from the instrumentation parts, representing the time-delay at the instrument devices. The second is related to the dynamic response of the patient time-delay.
2. The Smith Predictor Controller structure and the compensation of the time-delay.
3. The simulation and results using real data are then analysed and verified.

Chapter 6 investigates a PID-based robust deadbeat control technique in DoA control and proposes an application of the robust deadbeat technique to this system. This chapter comprises three main elements:

1. Consideration of the drug modeling and the distribution of the drug administered within the body, which leads to a pharmacokinetic and pharmacodynamic modeling and the prediction of the blood plasma concentration of the drug.

2. The basic structure of the robust deadbeat control system, the deadbeat controller coefficients, response times, the deadbeat controller design and derivation.
3. The robust deadbeat controller design for the depth of anaesthesia.

Chapter 7 describes the control of hypnosis using model predictive controller (MPC). The first part focuses on non-linear model predictive control to find the future optimal anaesthetic infusion sequence in order to minimize the desired output trajectory over a prediction horizon. The second part of this chapter details the simulation work as well analysing the results. This chapter coveres the following work:

1. A description of model predictive control technique, which focuses on the structure of the model predictive control.
2. A consideration of model predictive control design, which includes details of the constraints and the time horizons for depth of anaesthesia.
3. An analysis and evaluation of the simulation results.

Chapter 8 concludes the thesis and suggests further work.

CHAPTER 2

LITERATURE REVIEW

2.1 Background

The aim of this chapter is to introduce the problems related to the mathematical models employed in DoA feedback control. It also addresses the significance of this research.

A major gain of continuous intravenous drug infusion for general anaesthesia is the possibility of keeping a constant value of the effect concentration of the drug in use (Jensen et al. 2006). For DoA control the input, output, patient model and controller must be considered. Alonso et al. (2008) presented a method of target controlled infusion for neuromuscular blockade level of patients undergoing general anaesthesia. The estimates of the PK-PD model parameters are computed from data collected in the first 10 minutes, after a bolus is applied to the patient in the induction phase of anaesthesia (Alonso, Lemos & Mendonca 2008). Ionescu et al. (2008) presented a single-input (Propofol) single-output (Bispectral Index, BIS) model of a patient. The aim of the controller is to guarantee the stability in a desired range (Ionescu, et al. 2008). Absalom et al. produced a closed-loop control system of

anaesthesia that uses the BIS as the control variable to control the target blood concentration of the Propofol Target Controlled Infusion (TCI) system. The system was able to provide clinically sufficient anaesthesia in all patients, with enhanced accuracy of control. There was a tendency for more accurate control in those patients in whom the control algorithm incorporated effect-site steering (Absalom, & Kenny 2003). An algorithm was proposed for controlling the effect site concentration using a TCI method. The method limits the peak plasma concentration, thereby slowing the start of anaesthetic drug effect but potentially improving side effects. Simulation was used to observe the delay in time to peak effect for five types of anaesthetic drugs when the peak plasma concentration was limited by the algorithm (Van Poucke, Bravo & Shafer 2004). The control system was evaluated in 30 patient's cases. This study clearly suggests the desirability of individual tuning of the controller parameters.

2.2 Feedback Control of Anaesthesia

Feedback control of anaesthesia improves the quality of patient care at the same time reducing the administration and cost of anaesthetic medications. A method was presented by Mendonca & Lago (1998) for an enhanced tuning of the PID controller parameters to the patient's individual dynamics (Mendonca & Lago 1998). Auditory Evoked Potentials (AEP) has been reported to satisfy many requirements for measurement the level of anaesthesia. The AEP has been shown to provide good discrimination of the conversion from asleep to aware and vice versa. This system has been developed to obtain a single index which presents the morphology of the AEP and the index has been used as the input signal for closed-loop anaesthesia

during surgery in patients who did not receive neuromuscular blocking drugs (Kenny & Mantzaridis 1999).

In recent years, there have been increasing reports on DoA control using fuzzy. This is because it is a simple and effective technique for controlling non-linear and uncertain processes, and for dealing with imprecise, qualitative terms such as ‘‘low’’, ‘‘medium’’, or ‘‘high’’, rather than precise measurements. Fuzzy rules are a core element and have more effects than other elements in a fuzzy system because they dominate the primary performance. However, the derivation of fuzzy rules is a common bottleneck in the application of fuzzy control (Nunes et al. 2005). For classifying DoA and model patients' vital signs, Nunes et al (2005) developed a fuzzy relational classifier to classify a set of wavelet-extracted features from the AEP into different levels of DoA. They also developed a hybrid patient model using Takagi-Sugeno Kang fuzzy models (Nunes et al. 2005).

Chuang et al. (2009) provided two rule bases to control the administration of Cisatracurium, a non-depolarizing neuromuscular blocking agent. One rule base is extracted from the objective approach of the Fuzzy Modelling Algorithm (FMA), and another is from the subjective approach of expert's clinical experience. Shieh et al. (2006) defined evidence based on an adaptive genetic fuzzy clustering algorithm. A derived fuzzy knowledge model was proposed for quantitatively estimating the systolic arterial pressure (SAP), heart rate (HR), and Bispectral Index (BIS) using 12 patients. A hierarchical system has been developed to provide on-line advice on the concentration of inhaled volatile anaesthetics for depth of anaesthesia control. It merges on-line measurements (such as systolic arterial pressure and heart rate) and

clinical information (such as sweating, lacrimation and movement) using hierarchical architecture and self-organizing fuzzy logic for reasoning (Shieh, J. S., Linkens & Asbury 2005). In this study a computer screen-based simulator was developed to simulate the administration of intravenous and analgesic drugs. It merged on-line measurements (such as systolic arterial pressure (SAP) and heart rate (HR)) and non-numerical clinical signs (such as sweating, lacrimation and pupil response), using anaesthetists' experience or self-organizing fuzzy logic control (SOFLC) algorithms to administer drugs into a patient.

Voss et al. (1987) developed an adaptive algorithm to control multi-input/multi-output physiological systems and this method has been implemented and tested. The algorithm is a self-tuning controller that determines the input based on the expected difference between the actual output and desired output at a time interval equal to or greater than the system dead time. The algorithm was used to simultaneously control mean arterial pressure and cardiac output (CO) in anesthetized dogs by the simultaneous computer-controlled infusion of sodium nitroprusside and dobutamine. The results demonstrated the feasibility of using a advance moving average controller for multivariable drug delivery, but they also indicated the need for further work before clinical applications are attempted (Voss, Katona & Chizeck 1987).

Asteroth et al. (1997) established the feasibility of different real-valued reinforcement learning approaches for the task of multivariate adaptive control in anaesthesia. They also defined and explored the appropriateness of reinforcement learning systems for automation in anaesthesia (Asteroth, Moller & Schwilden 1997). Haddad et al. (2006) developed a direct adaptive control framework for

nonlinear uncertain nonnegative and compartmental systems with nonnegative control inputs. The framework was developed Lyapunov-based and guarantees partial asymptotic set-point regulation, that is, asymptotic set-point regulation with respect to that part of the closed-loop system states associated with the plant. A numerical example involving the infusion of the anaesthetic drug Propofol for maintaining a desired constant level of consciousness for non-cardiac surgery has also been provided to demonstrate the implementation of the proposed approach (Haddad, Hayakawa & Bailey 2006). The aim of the controllers is to supply an adequate drug administration treatment for Propofol to evade under or over dosing of the patients. These controllers aim to compensate for the patient's inherent drug response variability, to accomplish good output disturbance rejection, and to achieve good tracking to set point response (Dumont, Martinez & Ansermino 2009).

Janda et al. (2011) developed a closed-loop system to control the DoA and Neuromuscular Block (NMB) via the Bispectral Index and the Electromyogram (EMG) simultaneously, and evaluated the clinical performance of this combined system for general anaesthesia. The simultaneous closed-loop system using Propofol and Mivacurium was able to maintain the target values with a high level of precision in a clinical setting (Janda et al. 2011).

A PID controller was developed to control the closed-loop administration of Propofol and Remifentanil, using a BIS monitor (Liu et al. 2011). The controller was compared with manual Target-Controlled Infusion (TCI). During induction and maintenance of general anesthesia, the controller allows the automated delivery of

Propofol and Remifentanil and maintains BIS values better than manual administration (Liu et al. 2011).

2.3 Patient body Dynamics and Models

Many models in anaesthesia are based on relations between variables such us drug plasma level and effect. Models can establish a relationship between variables but may not explain the physical basis for the relationship (Beneken & van Oostrom 1998).

2.3.1 Body and interaction to anaesthetic medicine

Pharmacokinetic/pharmacodynamic modelings have made a substantial contribution to depth of anaesthesia by providing an insight into the factors affecting the onset and offset of drug effect (Schwilden & Olkkola 1991).

Pharmacokinetic interactions occur when the administration of one drug alters the disposition of another, and hence alters the concentration of drug at the receptor site, leading to an altered drug response. These changes in drug concentration at the receptor site may be produced by an alteration of (a) drug absorption and uptake into the body, (b) drug distribution, (c) drug metabolism and (d) drug elimination or excretion by nonmetabolic routes (Kennedy & Van Riji 1998; Naguib et al. 1998).

Schuttler et al. (2000) performed a multicentre population analysis to quantify the effects of covariates. Patients' inter- and intra-individual variability was estimated for clearances and volumes. The effects of age, weight, type of administration were investigated. A three-compartment model for pharmacokinetics of Propofol was described. It also found that weight had a significant covariate for elimination

clearance, the two inter-compartmental clearances, the volumes of the central compartment, the shallow peripheral compartment, and the deep peripheral compartment.

Minto et al. (2008) described the influence of cardiac output on the disposition of intravenous drugs within the first few minutes after administration of the anaesthetic. They also calculated intravenous loading doses that allow for the delay between the concentration of the anaesthetic in the plasma and the rising concentration at the site of drug effect. A stable level of drug effect using computerized infusion pumps that target the site of drug effect rather than the plasma was also achieved and maintained. Importantly, to consider models of drug interaction, an understanding of how drug offset varies with duration of administration is required (Minto & Schnider 2008).

Copeland et al. (2008) determined whether general anesthesia affected the entire body and/or the local (heart and brain) pharmacokinetics of each regional anesthetic. Their secondary objectives were to determine whether anesthesia affected their blood binding, tissue concentrations, or the pharmacokinetics of the racemic regional drugs enantioselectively (Copeland et al. 2008).

2.3.2 Patient body kinetics

A model has been defined as a concept of reality, which accounts for those properties of a phenomenon that are pertinent to the function of the model. Models are used in anesthesia to identify the various physiologic, pharmacological and physical processes that happen during general anaesthesia. Beneken et al. (1998) introduced the reader to some of the types of models that had been used to facilitate education

and research in anaesthesia. They also elucidate the steps involved in developing a model and the various types of models that have proven useful (Beneken & van Oostrom 1998).

Patient pharmacokinetics can be described by a two, three, and four-compartment model. Adjusting pharmacokinetics to each patient should improve the accuracy of target-controlled infusion and help to extend the field of application for target-controlled infusion (Bouillon et al. 1999). The earliest information about the composition of the human body was based on chemical analyses of specific organs, and rarely of the whole body. Development and application of the classic two-compartment model of body composition have accelerated in recent years because of the association of excess body fat with increased risk for cardiovascular diseases (Ellis 2000).

A review study was structured from the methodological point of view by Ellis in 2000. The relations between the various in vivo methods (densitometry, dilution, bioelectrical impedance and conductance (Ellis 2000), whole body counting, neutron activation, X-ray absorptiometry, computer tomography, and magnetic resonance imaging) and the five-level multicompartment model of body composition were described, along with the limitations and advantages of each method. This review also provided an overview of the current status of research in human biology, including examples of reference body composition data for infants, children, adolescents, and adults (Ellis 2000).

2.3.3 Patient body dynamics

A dynamic system is a system whose states are determined by the initial conditions and the temporal history of the inputs after the initialization. The temporal evolution of its states are mathematically formalized and written as differential equations for continuous and difference equation for discrete systems.

The purpose of a dynamic systems assumption is that the instantaneous configuration of a process is represented as a state in a space of states, the ”state space”. The temporal evolution of the process can be represented as the motion of the state in the state space, called orbit or trajectory. The element of the state space is defined by the number of state varaibles, which allows specifying uniquely the system’s behaviour at each point in-time. If the dimension is low enough, it can visualize the trajectory (De Feo 2001).

2.3.4 Models for control

The distribution of anaesthetic medications in the body depends on transport and metabolic processes (Bibian et al. 2003). Diverse models have been proposed for modeling the drug effect, such as experimental models, compartmental models and physiological models (Mahfouf, M., Asbury & Linkens 2003). The standard modeling paradigm that has been commonly used to describe the relationships between anaesthetic inputs and patient output indicators is that of compartment models (Bamdadian, Towhidkhah & Moradi 2008; Chilcoat 1980).

Another major aspect is the stability of the controller with respect to artefacts. If there is sensor failure, methods of PID control cannot predict the future dose needs

that maintain the anaesthetic effect within reasonable margins. The model-based controller can, however, be used to estimate the drug requirement during a period of failure when no feedback is possible. This is done on the basis of the adapted pharmacokinetic-dynamic model (Schwilden & Olkkola 1991).

The compartmental model is widely used in controlling of drug administration. Also, the non-linear three-compartmental patient model was used for the disposition of the Propofol (Eshghi, Aliyari & Teshnehlab 2009).

2.4 Control Techniques for DoA

The closed-loop control in medication was pioneered by Bamdadian et al. (2008) and Caelen et al. (2006) who established through clinical experiments that this form of control is secure, helpful, effective and in many cases better than manual control (Bamdadian, Towhidkhah & Moradi 2008; Caelen et al. 2006).

Huge patient-to-patient variations in dynamic model parameters must be accommodated. This is compounded by the large time-varying parameters for each patient through the course of a surgery, which makes it even more difficult to design a fixed-parameter PID controller that is suitable in many cases. It indicates the need for more investigations into robust control strategies. In addition, model-based control algorithms may be more useful in this case. Intelligent systems can provide the best structure to develop robust predictive controllers for clinical pharmacology. The previous efforts to develop close-loop control of general intravenous anaesthesia with Propofol have used a classic adaptive controller for compartmental model and BIS scale to measure the depth of anaesthesia (Eshghi, Aliyari & Teshnehlab 2009).

2.4.1 Model based predictive control in DoA

The concept of automated anaesthetic drug delivery has been investigated for 50 years (Steil & Rebrin 2005). However, despite many recent studies and clinical trials, no real clinical breakthrough has been achieved. New advances in nervous system monitoring technology have yielded a new set of real-time sensors to capture the effect of these drugs on the patient's state (Steil & Rebrin 2005). As a result, automated feedback control of anaesthetic drug delivery to a pre-defined set point can potentially provide the patient with a titration specifically adjusted to his or her needs.

Propofol is a common intravenous anaesthetic drug, used for both induction and maintenance of general anaesthesia during surgical operations because of its favourable pharmacokinetic profile and its inhibition of post-operative nausea and vomiting. Many closed-loop feedback systems for Propofol infusion have been proposed in the literature. Frei et al. (1999) designed a model predictive control algorithm from rule based and physiological models were shown for the regulation of respiratory functions and cardiovascular activity. The controllers have been compared to manual operations on real patients, indicating higher quality anaesthesia for the set of patients handled by the controller (Frei et al. 1999).

Rao et al. (2003) designed and developed a model-based control methodology for automatic regulation of mean arterial pressure and cardiac output in critical care using inotropic and vasoactive medications. The control algorithm has been used in a multiple-model adaptive approach in model predictive control structure to account for variability and explicitly handle anaesthetic rate constraints. The controller

performed better compared to experiments on manual regulation of the hemodynamic variables (Rao, Aufderheide & Bequette 1999 or; 2003). Gentilini et al. (2002) developed a model predictive control approach for the regulation of analgesia by infusing Alfentanil with MAP as the controlled variable. The proposed control was successful in the clinical setting. This method confirmed the possibility of achieving better hemodynamic control with the drugs that contains opium (Gentilini et al. 2002). Hoeven et al. (2007) described a design of a model of control system for a gas composition of the inhaled breath during anaesthesia. The control system was used to create an artificial breathing pattern, and a mechanical lung is used as a model of the human lung. Fresh gas was added close to the lung to create a rapid response, and sensors measured the properties of the gas mixture passing into the lung (Hoeven van der et al. 2007). Nicolas et al. (2008) developed a model to represent a patient subjected to general anaesthesia considering only the DoA. The model was built using MATLAB/SIMULINK. The algorithm was improved to be able to switch between two internal models. The plant (the patient model) was exactly one of these two models, then, the algorithm was modified to integrate a Model Predictive Control law instead of constant one (Cardoso & Lemos 2008; Furutani et al. 2010).

Authors evaluated a novel model predictive controller for closed-loop administration of Alfentanil via mean arterial blood pressure and predicted plasma Alfentanil concentration (Cp Alf) as input parameters. They evaluated and described a model predictive controller for the control of mean arterial pressure (MAP) as a primary and predicted plasma and Alfentanil concentration (Cp Alf) as a secondary input variable

for optimal dosing of an Alfentanil infusion rate (output variable) under the condition of a hypnotic state defined according to BIS.(Luginbühl et al. 2006).

Sawaguchi et al developed a hypnosis control system, which administers Propofol to regulate the BIS. Their study discussed three functions. First, a feedback controller using a MPC method which accommodated the effects of time-delays. Second, it dealt with a parameter estimation function of individual differences. Third, it discussed with a risk control function for preventing undesirable states such as drug over-infusion or intraoperative arousal (Sawaguchi et al. 2008).

Yelneedi et al. (2009) also developed an advance control strategy for the regulation of hypnosis with Propofol. A reliable PK-PD model with associated parameters was obtained and the closed-loop response for four different types of control methods (model predictive control, internal model control, controller with modelling error compensation, and proportional-integral-derivative (PID) control) were compared. The performances of these controllers were considered alongside with the performance of the conventional PID controller. The developed, model-based controllers were robust to inter-patient variability, and better at handling disturbances and amount noise (Yelneedi, Samavedham & Rangaiah 2009).

2.4.2 Time-delay in DoA control

The instrumentation and drug distribution time-delays are important factors for monitoring during surgery, especially in DoA for detection of awareness. Increasing the period of responsiveness increases the risk of recall (Dutton, Smith & Smith 1995a). Intra-operative awareness is a rare phenomenon during general anaesthesia with an incidence of between 0.1 and 0.2% (Dutton, Smith & Smith 1995b, 1995a)

and the existing monitors cannot dependably predict awareness in advance. However, a monitor should at least be able to detect a consciousness reaction. Zanner et al. (2009) showed that all currently available monitors need varying periods to determine a new index when reacting to changes in anaesthetic depth. The exact time-delay for the calculation of new index values is unknown (Zanner et al. 2009).

Several studies have been proposed in the literature investigating the effect of the time-delay during anaesthesia to improve intra-operative administration. Pilge et al. (2006) proposed a study based on the electroencephalographic analysis. Several parameters are used as a measure of the hypnotic component of anaesthesia. The time-delay of the tested indices limits the value in prevention of the recall of intra-operative events (Pilge et al. 2006).

The problem of time-delay estimation in depth of anaesthesia systems has been addressed with the focus on the practical applicability of methods. Four time-delay estimators have been described: a cross correlation method and three increasingly sophisticated interpretations of the phase spectrum, ranging from a point wise interpretation of the phase spectrum in terms of a delay to a Hilbert transform method (Müller et al. 2003). Muñoz et al. (2004) measured the time to peak effect of Propofol in children and adults. While this time is considerably longer in children, the finally calculated k_{e0} is particular to the model used to derive this parameter.

The k_{e0} obtained from the models of Kataria and the Paedfusor for Propofol in children can be used with caution with the corresponding models to target effect site concentration of Propofol in children. They theoretically proved that the effect site is

a more logical target than plasma. As a result, this reduces the delay to obtain a given drug effect and possibly also its variability, when compared with plasma concentration (Muñoz et al. 2004). Heyse et al. (2009) based on the available literature presented a method to compare monitors of the hypnotic component of anaesthesia (Heyse et al. 2009). Michel et al. (2001) worked on the monitoring of anaesthetic depth. The aim of their study was to compare the accuracy of this new index with the Bispectral Index (BIS), to predicted effect-site concentration of propofol, and hemodynamic measures and the time-delay (Struys et al. 2001). Ionescu et al. (2011) introduced the cross-correlation analysis to estimate the time-delay originating from instrumentation in intensive care unit of anaesthesia. The algorithm was tested on synthetic signals, ensuring its accuracy for online estimation purposes (Ionescu, Hodrea & De Keyser 2011).

2.4.3 Deadbeat control in DoA

The robust deadbeat control scheme is simpler and the performance is better (Wen & Lu 2008). In addition, this control scheme does not include any complicated math and calculation except the normalisation and look-up table. It is easily accepted by industrial designers (Emami-Naeini & Franklin 1982).

Malesani et al. (1999) presented a theoretical analysis of the stability robustness of the dead-beat control technique with respect to parameter mismatches. These are very likely to be encountered when considering active filter and rectifier applications of current-controlled voltage-source converters. The authors proposed an effective analysis technique, which enables one to predict the occurrence of instability problems, revealing the different robustness levels of the possible implementations of the converter's dead-beat control. The effectiveness of the theoretical analysis and of

the proposed improvements have been verified by simulations and experimental tests on a laboratory pulse width modulator (PWM) rectifier (Malesani, Mattavelli & Buso 1999).

A new approach for deadbeat control was presented by Zhang et al. (1999), in which the estimation of the disturbance was carried out with a repetitive predictor instead of a disturbance observer. Taking advantage of repetitiveness of the loads, it gave better performance at lower sampling frequency. Simulations and experiments confirmed the advantages of this method (Zhang, Kai et al. 1999).

A considered control approach is based on the combination of dead-beat control of inverter currents and space vector modulation. Simulations and experimental tests show that the intrinsic calculation delay of the dead-beat algorithm represents a serious hurdle for the accomplishment of an acceptable compensation quality. From the stability point of view, the effects of parameter mismatches on the system's performance are investigated by means of a complete eigenvalue analysis, which reveals the limits of the system's stability for different possible implementations of the considered control strategy (Malesani, Mattavelli & Buso 1998).

A proposed method of a simple tuning algorithm for digital deadbeat control based on error correlation has been investigated. The proposed solution was simple, it required a short tuning time, and it was appropriate for different dc–dc converter topologies (Saggini et al. 2007).

2.5 Summary

Anaesthetists have succeeded in creating anaesthesia as a secure procedure. However, the present practice relies uniquely on secondary signs to warn the practitioner of either pharmacological toxicity or anesthetic inadequacy. On the other hand, much research into the closed-loop control of anaesthesia has not been adopted and yet not acknowledged for routine use.

In the past 15 years, serious advances have been made. In 1996, practitioners had access to monitors to measure the degree of anaesthesia-induced unconsciousness. Monitors, such as the BIS, are still considered by anesthetists to be nothing more than gadgets. In addition, the BIS sensor price discourages the use of monitors in everyday practice.

This literature review shows that many methods have been developed to design control systems with input and state constraints however; these methods do not give satisfactory performance in many situations. This leaves scope for the development of new strategies, particularly to control systems with constraints. This research will result in development of new control methods and algorithms, which can be used in various sectors to control systems more effectively. This research will also state the performance criterion thereby mentioning the limitations the new methods may have. In addition, the performance of the new methods will be validated in simulation experiment.

CHAPTER 3

HUMAN BODY AND MODELS

3.1 Kinetics and Dynamics of Human Body

There are several methods for the modelling of a biological system for anaesthetic distribution, however the physiological mechanisms of drug circulation and drug effects are only partially known (Gentilini, et al. 2001). As a result, a first principle modeling is almost impossible. Therefore, one has to decide on approximate first principle physiological models (Bischoff 1975), black-box identification schemes (Jacobs 1988), and information based modeling. Each approache has certain drawbacks. In physiological models, parameters are uncertain as they collected from different sources where experiments may have been performed under different conditions (Bailey & Shafer 1991). Black-box models and knowledge based models suffer from poor extrapolation properties (Gentilini, et al. 2001).

Experimental models are black box models (see in Figure 3.1) and relate input and output by an analytical term, such as a sum of exponentials (Carson & Jones 1979).

Compartmental models are formulated based on the minimum number of compartments that effectively fit observed data (Sadean & Glass 2009). Physiologically based models are the most realistic representation of drug kinetics, for the reason that the parameters relate directly to physiology, anatomy and biochemistry. Clearly all forms are experimental and the above definitions specify the approach of formulating the model rather than the resulting model. All formulations give a set of ordinary differential equations describing the explicit drug characteristics. The major two forms used in anaesthesia are compartmental and physiological models. The models have mismatches, which comprise individual differences in the pharmacokinetic-pharmacodynamic (PK-PD) parameter values and estimation error in the pharmacodynamic parameters. If the model is used in an open loop controller, these mismatches produce fluctuation of the BIS. The effects of these mismatches can attenuate in closed-loop systems. However, more accurate model improves the tracking ability and robust stability of the closed-loop control systems (Schnider et al. 1999). The PK is identified on the basis of input-output data sequences. An input drug is administered and the time course is measured by taking blood samples. The infusion time of the bolus is generally neglected and therefore the response can be viewed as an approximation of an impulse response. The blood (or more appropriately, plasma) compartments are used as central compartment (compartment 1). The effect-site concentration is only used to account for the time lag between drug concentration and drug effect (Schnider et al. 1999).

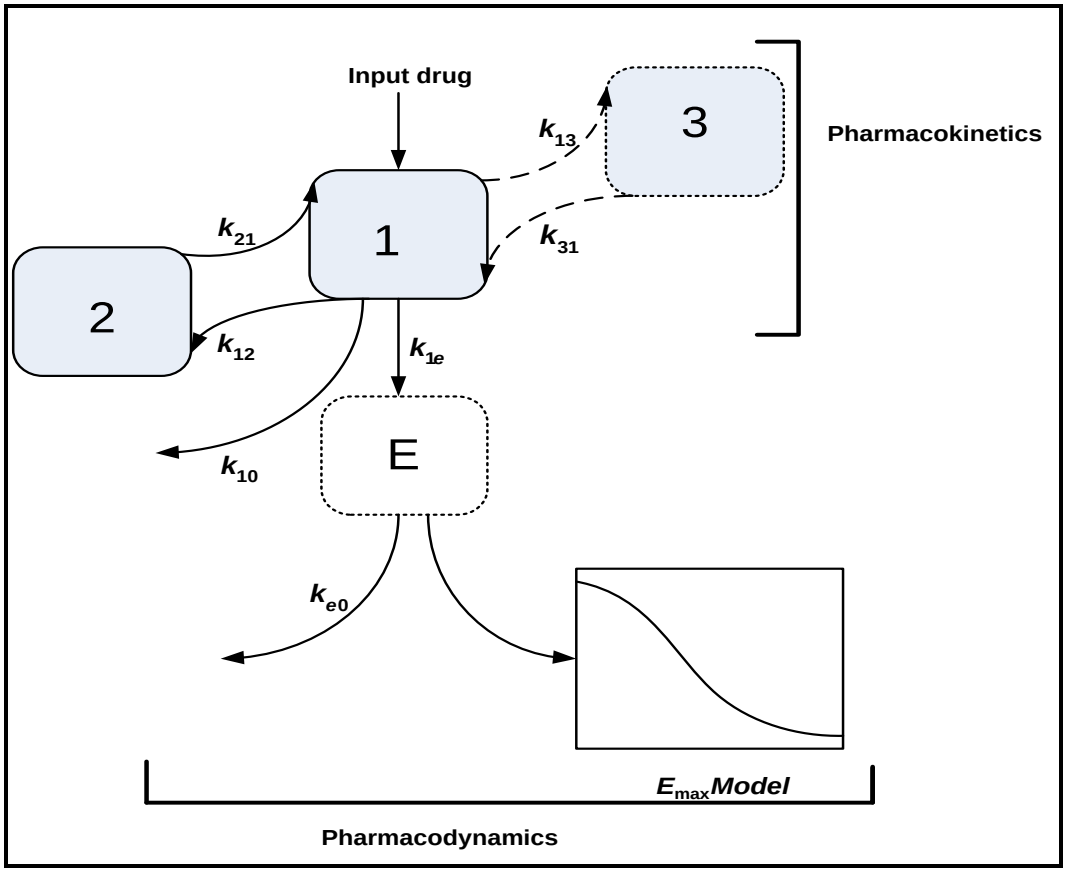

Figure 3.1: Human body modeling

3.2 Pharmacokinetic Model

Pharmacokinetics (PK) is the dynamic process of drug distribution in the body (Sheiner & Steimer 2000). The construction of the pharmacokinetic model is based on the population of pharmacokinetic model given through a large-scale multicenter research described by Schnider et al. (1998; 1999), Minto et al. (1997), and Schnider & Shafer (1997). The patient's age and weight are included in this model and it seems to be sufficiently dependable, but this model does not include the effect site that relates directly to the BIS (Shafer & Gregg 1992).

The human body modeling is divided into a number of compartments to drive the PK model (Cardoso & Lemos 2008). In each part of these compartments, the drug concentration is homogeneous. The type of the anaesthetic is Propofol.

We consider a unified model that can deal with both bolus and continuous infusion and has the effect-site compartment.

The pharmacokinetic model is represented by the following equations:

$$\begin{bmatrix} \dot{x}_1(t) \\ \dot{x}_2(t) \\ \dot{x}_3(t) \end{bmatrix} = A_1 \begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{bmatrix} + B_1 u(t) \tag{3.1}$$

where

$$A_1 = \begin{bmatrix} \frac{-k_{10} - k_{12} - k_{13}}{V_1} & \frac{k_{21}}{V_1} & \frac{k_{31}}{V_1} \\ \frac{k_{12}}{V_2} & \frac{-k_{21}}{V_2} & \frac{0}{V_2} \\ \frac{k_{13}}{V_3} & \frac{0}{V_3} & \frac{-k_{31}}{V_3} \end{bmatrix}$$

$$B_1 = \begin{bmatrix} \frac{1}{V_1} \\ 0 \\ 0 \end{bmatrix}$$

where $x_1(t)[mg]$ denotes the drug amount in the central compartment. $\frac{x_1}{V_1}$ is the blood concenration. The peripheral compartments 2 and 3 represent the drug exchange of the blood with body tissues. The masses of drug in fast and slow (the concentration of Propofol) equilibrating peripheral compartments are expressed by x_2 and x_3. In addition, $u(t)[\frac{mg}{s}]$ is the infusion rate of the anesthetic (Propofol) drug into the central compartment (the manipulated variable) (Niño et al. 2009). The

parameters k_{ji} $(i \neq j)$ and V_i are the clearance and volume of compartment i, respectively, given by functions of the patient's age and weight, height and gender (Marsh et al. 1991) and can be calculated for Propofol as shown in Table 3.1:

Table 3.1: Pharmacokinetic parameter values (Niño et al. 2009).

$V_i[l]$	$C_{li}[l/min]$
$V_1 = 4.27$	$Cl_1 = 1.89 + 0.0456(weight - 77) - 0.0681(lbm - 59) + 0.0264(height - 177)$
$V_2 = 18.9 - 0.391(age - 53)$	$Cl_2 = 1.29 - 0.024(age - 53)$
$V_3 = 2.38$	$Cl_3 = 0.836$

$$\begin{bmatrix} k_{10} \\ k_{12} \\ k_{13} \\ k_{21} \\ k_{31} \end{bmatrix} = \begin{bmatrix} 1/V_1 & 0 & 0 \\ 0 & 1/V_1 & 0 \\ 0 & 0 & 1/V_1 \\ 0 & 1/V_2 & 0 \\ 0 & 0 & 1/V_3 \end{bmatrix} \begin{bmatrix} Cl_1 \\ Cl_2 \\ Cl_3 \end{bmatrix} \tag{3.2}$$

From equation (3.2) and Table 3.1, the parameters Cl_i are calculated as follows:

$$\begin{bmatrix} Cl_1 \\ Cl_2 \\ Cl_3 \end{bmatrix} = \begin{bmatrix} 0.0456 & 0.0264 & -0.0681 & 0 \\ 0 & 0 & 0 & -0.024 \\ 0 & 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} weight \\ heigh \\ lbm \\ age \end{bmatrix} + \begin{bmatrix} -2.271 \\ 0.018 \\ 0.836 \end{bmatrix}$$

(3.3)

where weight, height and age are kg, cm and years, respectively.

The patient body mass (lbm) for men (m) and women (f) is considered in the following expressions (Ionescu, De Keyser & Struys 2011):

$$\begin{bmatrix} \mathrm{lbm}_m \\ \mathrm{lbm}_f \end{bmatrix} = \begin{bmatrix} \mathrm{m} & 0 \\ 0 & \mathrm{f} \end{bmatrix} \begin{bmatrix} 1.1 & -128 \\ 1.07 & -148 \end{bmatrix} \begin{bmatrix} \mathrm{weight} \\ (\mathrm{weight}/\mathrm{heigh})^2 \end{bmatrix} \tag{3.4}$$

A three-compartment model can describe the PK of Propofol well. Insertion of age and weight as covariates considerably improved the model. Adjusting PK for each person should improve the accuracy of the target-controlled infusion and may help to extend the field of application for target-controlled infusion Propofol of DoA for both induction and maintenance.

3.3 Pharmacodynamic Model

Pharmacodynamics (PD) means the description of the effect of the drug on the body. A PD model presented as a low-pass filter is used to relate the plasma Propofol concentration $\mathrm{C_p^{prop}}$ (represented by $\mathrm{x_1}$) in the blood and the Propofol effect site concentration $\mathrm{C_e^{prop}}$. This yields the following state space representation:

$$\mathrm{C_p} = \mathrm{C_1 x_1} \tag{3.5}$$

$$\dot{\mathrm{x}}_\mathrm{e} = \dot{\mathrm{C}}_\mathrm{e} = -\mathrm{A_2 x_2} + \mathrm{B_2 x_1} \tag{3.6}$$

where $A_2 = K_{e0}$, $B_2 = K_{1e}$.and $\mathrm{x_2} = \mathrm{x_e}$

The amount of K_{e0} and K_{1e} are constants and $\mathrm{x_2}$ represents the drug in the effect compartment. The constant $K_{e0} = K_{1e}$ in equation 3.6 is 0.456 [$\mathrm{min^{-1}}$] for Propofol (Schnider et al. 1998; Schnider et al. 1999). The effect site compartment is a very

small compartment has a negligible impact related to the central compartment (Shafer, S. et al. 1998).

where $C_e$is:

$$C_e(s) = \frac{k_{e0}}{s+k_{e0}} C_p(s) \tag{3.7}$$

The Hill equation is an equation used in biochemical characterization. It consists of a static model with one (or two) input and one output (the DoA).

The Hill equation (Bailey & Haddad 2005) is given by:

$$E(s) = E_0 - E_{max} \frac{C_e^{\gamma}(s)}{EC_{50}^{\gamma}+C_e^{\gamma}(s)} \tag{3.8}$$

E_0 represent the conscious state without anaesthetic, which is assigned a value of 100; E_{max} denotes the maximum effect achieved by the anaesthetic infusion; C_{50} is the drug concentration at 50% of maximal effect and represents the patient's sensitivity to the drug; and γ represents the steepness of the static nonlinearity. A very important advantage of continuous drug infusion for general anaesthesia is the opportunity to maintain a nearly constant rate of the effect concentration of the drug in use (Mahfouf, et al. 2005).

3.4 Time-Delay in Response

Computational delays and sampling effects can critically affect the performance of a control system. Typically, the closed-loop responses of a system become oscillatory and unstable if these factors are not taken into account. Therefore, when modeling a control system, one should include computational delays and sampling effects to

accurately design and simulate a closed-loop system (Franklin, Powell & Emami-Naeini 1994).

The process of anaesthesia is nonlinear with time-delay. There are also some constraints in calculating administrative drug dosage which have to be included (Ionescu, De Keyser & Struys 2011). Drug concentration in the patient's body is estimated and this estimation is used in the patient's model for controlling the depth of anaesthesia (Rezvanian et al. 2011).

Propofol infusion to the BIS includes considerable time-delay. This delay is caused by the movement of Propofol from a three-way stopcock to the patient's body in an intravenous fluid line and circulation of Propofol in blood vessels at the central compartment. The delay shown by the BIS monitor is between 15–60 s (Pilge et al. 2006; Zanner et al. 2009).

The BIS value BIS(t) was determined by the past value of the effect site concentration, as shown in equation 3.9, where τ is the time-delay.

$$\mathrm{BIS}(t) = m \cdot C_e(t - \tau) + c \tag{3.9}$$

3.5 Intra-patient Uncertainty

Intra-patient variability clearly indicates the variability observed in the drug response within one particular subject. This variability originates from different factors. The pharmacokinetics of intravenous agents differs depending on the method of the drug administration bolus or infusion. PK models have the same steady state gain whether

bolus or infusion is used. The initial peak plasma concentration following a bolus administration is significantly over-predicted by the corresponding infusion model (see Figure 3.2) (Schüttler & Ihmsen 2000; Yelneedi, Lakshminarayanan & Rangaiah 2009).

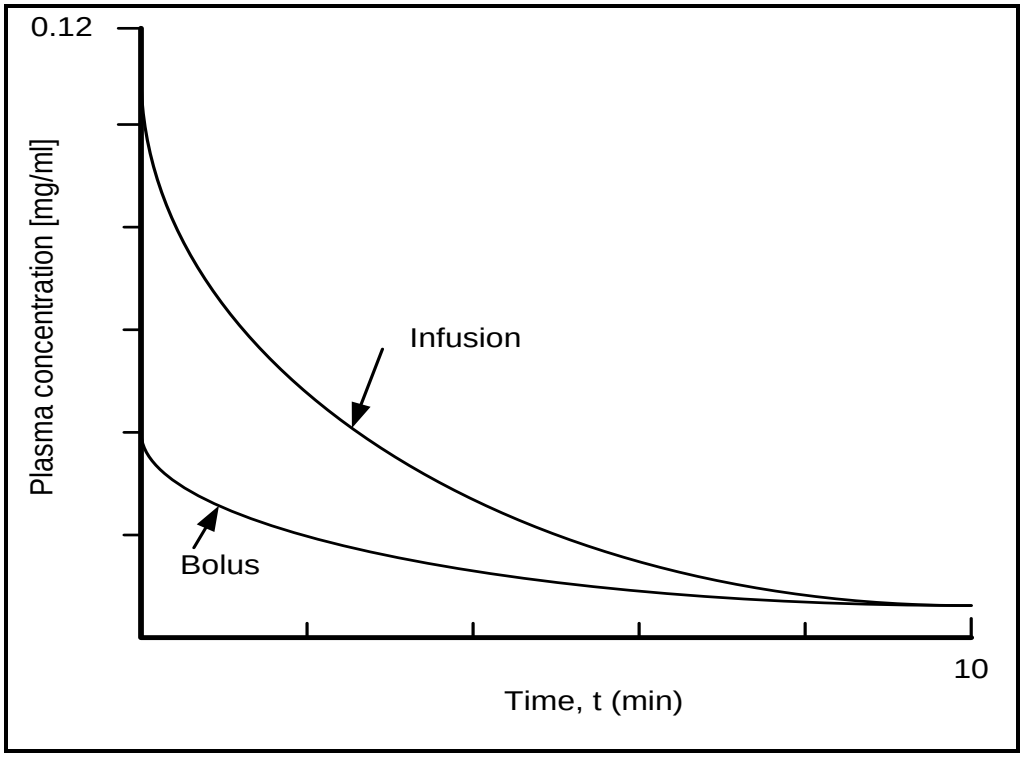

Figure 3.2: Bolus vs infusion pharmacokinetic of propofol (Niño et al. 2009)

For small setpoint changes with/without disturbances, the controller will manage propofol infusion at a rate approximately 0.5 ($mg/min \cdot kg$) during steady state. Within this range the Propofol pharmacokinetics is expected to be accurately described by the infusion model. In some cases the controller must signal an increase in output infusion rates when the transients are above 1 ($mg/min \cdot kg$) (Dumont, Martinez & Ansermino 2009).

Importantly, the propofol amount and distribution may track and follow the behavior observed for bolus regulations. If the controller output is not constrained to the

infusion rates up to 0.5 $(mg/min \cdot kg)$, then the controller design has to take into account the difference between the bolus and infusion in the dynamic of PK models. This difference in bolus and infusion models creates a system uncertainty. Tables 3.4a and 3.4b show bolus infusion variation for individual cases (Bibian 2006). Another factor is the controller setpoint. The Hill saturation may be viewed as a gain that is dependent on the operating point of the system.

In PK-PD modeling, it is usual to distinguish between two different sorts of uncertainty, the first is the uncertainty originating from intra-patient variability (for instance the variability observed within one particular individual) and the second is uncertainty caused by inter-patient variability such as the variability observed between different persons (Bibian 2006). NON linear Mixed Effect Models (NONMEM) is a project group, from the University of California, San Francisco, Canada. One of the major advantages of NONMEM group is that inter-patient and intra-patient variability can be quantified.

The intra-patient variability describes the residual errors resulting from assay errors, time-recording inaccuracy and model misspecification (Schüttler & Ihmsen 2000). The model for intra-patient variability assumes that the error increases with increasing concentrations, but this error should be centered around zero. This estimation indicates nonlinear for the pharmacokinetics of Propofol, which means that total body clearance decreases with increasing concentration (Bailey & Haddad 2005).

Schüttler et al. (2000) in their study spanning hundreds of patients and thousands of blood samples, provides the most up-to-date intra-patient variability which was found to be less than 20%. Their PK parameters are presented in the Table 3.2 and Table 3.3 (Schüttler & Ihmsen 2000).

Table 3.2: Parameter estimates from the NONMEM analysis (Schüttler & Ihmsen 2000).

Parameters estimation	Value	Units	SE
θ_1	1.44	[l · min]	0.09
θ_2	9.3	[l]	0.9
θ_3	2.25	[l · min]	0.31
θ_4	44.2	[l]	6.1
θ_5	0.92	[l · min]	0.15
θ_6	266	[l]	43
θ_7	0.75		0.06
θ_8	0.62		0.09
θ_9	0.61		0.11
θ_{10}	0.045		0.012
θ_{11}	0.55		0.13
θ_{12}	0.71		0.26
θ_{13}	-0.39		0.15
θ_{14}	-0.40		0.10
θ_{15}	1.61		0.36
θ_{16}	2.02		0.41
θ_{17}	0.73		0.23
θ_{18}	-0.48		0.12

Table 3.3: Propofol P K parameter sets from (Schüttler & Ihmsen 2000).

PK parameters	Value	Units
Cl_1	$\theta_1 \cdot (BW/70)^{\theta_7}$ if age ≤ 60	$[l \cdot min^{-1}]$
	$\theta_1 \cdot (BW/70)^{\theta_7} - (age - 60) \cdot \theta_{10}$ if age > 60	$[l \cdot min^{-1}]$
Cl_2	$\theta_3 \cdot (BW/70)^{\theta_8} \cdot (1 + ven \cdot \theta_{14}) \cdot (1 + bol \cdot \theta_{16})$	$[l \cdot min^{-1}]$
Cl_3	$\theta_5 \cdot (BW/70)^{\theta_{11}} \cdot (1 + bol \cdot \theta_{18})$	$[l \cdot min^{-1}]$
V_1	$\theta_2 \cdot (BW/70)^{\theta_{12}} \cdot (age/30)^{\theta_{13}} \cdot (1 + bol \cdot \theta_{15})$	[l]
V_2	$\theta_4 \cdot (BW/70)^{\theta_9} \cdot (1 + bol \cdot \theta_{17})$	[l]
V_3	θ_6	[l]

3.6 Inter-patient Uncertainty

Due to inter-patient pharmacodynamic variability, close-loop controllers have not been widely adopted clinically because control of anaesthetic concentration does not translate into control of anaesthetic effect (Bailey & Haddad 2005). Inter-patient variability (system uncertainty), non-linearity, and time-delays reveal the challenges inherent in biological systems (Niño et al. 2009).

From (3.6) and (3.8) it can be seen that the drug effect is a function of the pharmacokinetic parameters as well as the pharmacodynamic parameters. If these parameters are known, it is straightforward and uncomplicated to calculate the dose procedure needed to achieve the target BIS signal. Because of the uncertainties in the pharmacokinetic and pharmacodynamic parameters due to inter-patient variability, these parameters are not known for each patient, and inter-patient variability may be significant. For some parameters the estimation for the coefficients of variability are as high as 100% (Haddad, Hayakawa & Bailey 2006).

In Tables 3.4a and 3.4b, the data of American Society of Anaesthesiologists (ASA) shows that two patients with the same physiological characteristics (age, weight, lean body mass) can have largely different PK-PD parameters. For example, patient

number 15 in Table 3.4a (female, 21 yrs old, 53 kg, 157 cm, ASA I) and patient number 53 (female, 21 yrs old, 67 kg, 163 cm, ASA I) have considerably different PK time-delay (45 sec vs. 4 sec), EC50 parameter (3.8 µg/ml vs. 2.3 µg/ml), and saturation characteristics (Hill steepness of 1.2 vs. 2.5).

Table 3.4a: PD models obtained (Bibian 2006)

Patient	Traditional PD approach			Proposed PD approach			
	LTI	Hill		LTI			Hill
	Ke0$[s^{-1} \cdot 10^{-3}]$	EC50 [µg/ml]	γ	T_d [s]	k_d $[s^{-1} \cdot 10^{-3}]$	EC_{50}[µg/ml]	γ
G I: >18 - <30 years							
007	10.0	1.8	2.9	22	133.5	3.2	4.7
008	13.8	2.7	3.2	4	44.4	3.1	2.5
010	0.8	0.4	3.3	44	25.0	2.4	1.9
015	1.9	1.1	1.8	45	51.5	3.8	1.2
016	4.2	1.7	1.9	39	85.7	3.8	2.3
023	10.7	3.1	2.8	18	82.5	3.9	2.1
030	5.6	1.8	3.1	32	44.4	2.9	2.8
035	8.4	1.9	3.8	12	26.7	1.9	2.3
038	11.8	3.0	2.6	7	35.2	3.4	1.9
046	9.9	2.4	3.9	9	32.8	2.8	2.8
048	8.6	2.2	3.3	17	46.4	2.8	2.3
053	9.9	2.1	3.4	4	26.2	2.4	2.5
058	10.6	1.9	3.0	9	50.4	2.5	2.6
066	12.9	2.4	2.4	18	160.5	3.6	3.9
071	8.1	1.8	2.7	20	75.0	2.5	1.9
Mean	8.5	2.0	2.9	20.0	61.4	3.0	2.5
SD	3.8	0.7	0.6	13.9	40.1	0.6	0. 8
G2: >30 - <40 years							
006	2.4	1.1	4.6	44	54.8	3.2	2.7
009	5.9	2.2	2.6	29	83.1	4.0	2.3
029	6.3	2.6	3.2	18	34.4	3.7	2.1
036	10.9	2.9	1.5	1	29.6	3.3	1.2
047	11.9	3.0	2.2	1	24.9	3.1	1.5
049	8.7	3.0	2.5	12	35.2	3.9	1.8
051	9.5	2.5	2.9	4	24.8	2.7	2.0
061	6.1	1.8	2.9	12	28.7	2.8	2.2
063	8.2	2.1	2.5	5	27.0	2.8	2.1
065	17.0	3.3	2.5	4	67.2	3.6	2.0
068	7.3	2.4	2.5	12	29.3	3.1	1.8
074	5.1	2.1	2.1	13	29.1	3.7	1.8
Mean	8.3	2.4	2.7	12.9	39.0	3.3	2.0
SD	3.8	0.6	0.7	12.6	19.0	0.4	0. 4

Table 3.4b: PD models obtained (Bibian 2006)

Patient	Traditional PD approach			Proposed PD approach			
	LTI	Hill		LTI			Hill
	Ke0[$s^{-1} \cdot 10^{-3}$]	EC50 [µg/ml]	γ	T_d [s]	k_d [$s^{-1} \cdot 10^{-3}$]	EC_{50}[µg/ml]	γ
G3: >40 - <50 years							
004	2.1	0.9	2.6	35	38.0	3.3	1.8
025	9.5	4.4	1.9	11	36.6	6.1	1.3
027	15.3	4.7	2.2	2	32.6	4.7	1.3
040	10.8	4.1	2.4	12	35.0	4.5	1.4
042	7.2	2.8	2.5	10	28.7	3.9	2.0
043	7.7	2.8	2.5	12	34.8	3.9	1.8
052	11.7	3.2	3.1	9	36.6	3.2	1.9
069	9.8	2.7	2.9	8	35.6	3.4	2.3
072	5.4	1.7	2.5	13	30.0	3.0	1.9
Mean	8. 8	3.0	2.5	12.4	34.2	4.0	1.7
SD	3. 8	1.2	0.4	9.1	3.1	1.0	0. 3
G4: >50 - <60 year018							
018	11.9	3.1	3.1	3	31.5	3.5	2.3
033	4.4	2.3	1.8	29	42.0	4.4	2.2
041	8.3	3.7	1.6	2	21.8	4.7	1.4
057	5.4	2.2	1.6	16	28.8	3.7	1.1
060	7.0	2.7	2.6	10	26.4	4.0	1.9
064	12.7	3.9	1.3	6	58.0	5.0	1.5
070	8.7	3.1	2.1	6	32.2	4.2	1.5
075	5.2	1.8	2.4	12	24.3	3.1	1.8
Mean	8.0	2.9	2.1	10.5	33.1	4.1	1.7
SD	3.1	0.7	0.6	8.8	11.8	0.7	0.4

Table 3.5: Propofol PK-PD inter-patient variability (Bibian 2006)

	Td				kd				EC50				γ			
	MIN	MAX	Td,0	u	MIN	MAX	Kd,0	u	MIN	MAX	Kd,0	u	MIN	MAX	γ	u
	[s]	[s]	[s]	[%]	[s^{-1}]	[s^{-1}]	[s^{-1}]	[%]	[µg/ml]	[µg/ml]	[µg/ml]	[%]	[l]	[l]	[l]	[%]
Age group																
G1	4	45	24.5	83.7	25.0	160.5	92.7	73.0	1.9	3.8	2.8	33.3	1.9	4.7	3.3	42.4
G2	1	44	22.5	95.6	24.8	83.1	53.9	54.0	2.8	4.0	3.4	17.6	1.2	2.7	1.9	38.5
G3	2	35	18.5	89.1	28.7	38.0	33.3	13.9	3.0	6.0	4.5	33.3	1.3	2.3	1.8	27.8
G4	2	29	15.5	87.1	21.8	58.0	39.9	45.4	3.1	5.1	4.1	24.4	1.1	2.3	1.7	35.3
Population	1	45	23	95.6	21.8	160.5	91.1	76.1	1.9	6.0	4.0	51.9	1.1	4.7	2.9	62.0

Table 3.6: Intra- and inter-patient variability (Bibian 2006)

	Td				kd				EC50				γ			
	MIN [s]	MAX [s]	Td,0 [s]	u [%]	MIN $[s^{-1}]$	MAX $[s^{-1}]$	Kd,0 $[s^{-1}]$	u [%]	MIN [µg/ml]	MAX [µg/ml]	Kd,0 [µg/ml]	u [%]	MIN [l]	MAX [l]	γ [l]	u [%]
patient																
1	23	29	26.0	11.6	17.4	67.9	42.7	59.2	17.2	22.1	19.7	12.5	1.4	1.6	1.5	6.7
2	15	23	20.5	12.2	30.5	46.2	38.4	20.5	14.5	15.9	15.2	4.6	1.5	1.8	1.7	9.1
3	8	17	13.5	25.9	48.5	81.5	65.0	25.4	15.3	21.5	18.4	13.8	1.3	1.6	1.5	10.3
4	25	45	35.0	28.6	26.0	39.8	32.9	20.1	16.4	21.4	18.9	13.2	1.6	2.1	1.8	33.5
5	25	42	33.5	25.4	37.1	214.0	125.5	70.5	20.2	28.2	10.2	16.5	1.2	1.5	1.4	7.1
Population	8	45	26.5	69.8	17.1	214.0	115.5	85.2	14.5	28.2	21.4	32.1	1.2	2.1	1.6	27.3

Considering the differences between PK-PD models obtained over a large population of patients, the inter-patient variability can be easily characterized. Table 3.4a and 3.4b provide a good representation of an adult population with respect to the response to propofol administration (Bibian 2006). The parametric variability observed between the different PK-PD models presented in tables 3.4a and 3.4b are shortened in Table 3.5.

As we can see, there is a considerable difference in the PK time-delay and PD time-constant between patients. At the same time as the $EC_{50,}$ variability is more limited, there is still a six-time difference in terms of the overall PK-PD steady-state gain. To quantify intra- versus inter-patient parametric variability, a clinical study was carried out in 2002 involving five patients receiving electro-convulsive shock therapy (ECT) (Bibian 2006). These patients were given a total of six treatments over two months.

Each treatment consisted of the administration of a single Thiopental induction dose to provoke a fast loss of consciousness before the application of the electric shock. The PK part of the model was derived based on a published Thiopental PK parameter set. The model parameters derived during these multiple repeats are presented in parametric uncertainty in Table 3.6.

3.7 Summary

In this chapter, the Pharmacokinatic and Pharmadynamic uncertainty are investigated. This uncertainty stems from both inter- and intra-patient variability in drug disposition and effect. The limition of the PK-PD models to a certain age bracket and constraining the control action to infusion reduce the uncertainty while not adding complexity to the controller design.

Recent advances in non-linear regression analysis have already allowed pharmacologists to characterize Pharmacokinatic parameters which account for the effect of the age, weight, gender. The large variability observed between patients and the discrepancies between the model parameters published in the literature explain the lack of enthusiasm in the anaesthesia community for Pharmacodynamic models. However, the poor performance of these models stems mostly from a poor choice of the model structure rather than an inherent limitation of the system.

CHAPTER 4

DOA INTERNAL MODEL CONTROL USING SIMPLIFIED PATIENT MODEL

4.1 Internal Model Control Technique

During surgery the anaesthetist carefully controls the delivery of anaesthesia given to the patient in an effort to attain and maintain a consistent and adequate level of DoA (Bamdadian, Towhidkhah & Moradi 2008). In this process, the anaesthetist is acting as a manual feedback controller (Dumont, Martinez & Ansermino 2009). As there are no direct means of assessing a patient's level of consciousness during surgery, the performance of the process relies on the experience of the anaesthetist (Weber et al. 2004). The decision for the initial anaesthetic level is generally made by using the recommended drug dosages based on different patient characteristics, such as age and weight (Alonso, Lemos & Mendonca 2008; Schüttler & Ihmsen 2000). The anaesthetist determines any subsequent alteration in

the anaesthetic level by observing physical signs from the patient (McAnulty, Robertshaw & Hall 2000). These physical signs, the indirect indicators of the DoA, may include changes in blood pressures or heart rate, lacrimation (the production of tears in the eyes), facial grimacing, muscular movements, spontaneous breathing, diaphoresis (sweating, especially sweating induced for medical reasons), and other signs that may predicate awareness (Bequette 2007). However, these are not reliable indicators of changes in patient level of consciousness. Although an anaesthetist can adjust recommended anaesthetic dosages based on individual patient characteristics, these adjustments cannot always account for variability in patient responses to anaesthesia or changes in anaesthetic requirements during the course of surgery (Bruhn 1999; Bruhn et al. 2006). Closed-loop administration of anaesthetics during surgery promises to supply a number of benefits such as minimising the over all amounts of drugs required to reduce recovery time, which also reduces cost and allowing the anaesthetist to focus on more critical safety tasks (Foster, Bojak & Liley 2008).

However, the feedback controls require schemes, a mathematical model of the patient, and drug delivery for the design and implementation. The proposed robust internal model control (RIMC) uses the approximate linear pharmacokinetic-pharmacodynamic (PK-PD) model in the controller design, and regulates the patient's Bispectral Index (BIS) by manipulating the infusion rate of propofol. Extensive simulations are conducted to investigate the robustness of the proposed RIMC controller, by considering parameter variations in the selected model to account for patient model mismatch. The proposed RIMC scheme has also been evaluated for disturbance rejections. The main contributions of this study are to

demonstrate the control of hypnosis using RIMC, and to compare its performance with the traditional PID controller.

4.2 Patient Model for IMC Control

As shown in Figure 4.1, the human body is generally divided into different parts of compartments to drive the pharmacokinetic (PK) model (Cardoso and Lemos, 2008). The DoA model considers both Propofol and Remifentanil since the latter has a non-negligible effect on the DoA level.

Hereafter, c_e^{remi} (the Remifentanil effect concentration) is assumed to be given and only the Propofol chain is considered. The Propofol infusion rate "r^{prop}" is called "u"

where u is the manipulated variable. This yields the continuous linear state space model given in equation 4.1.

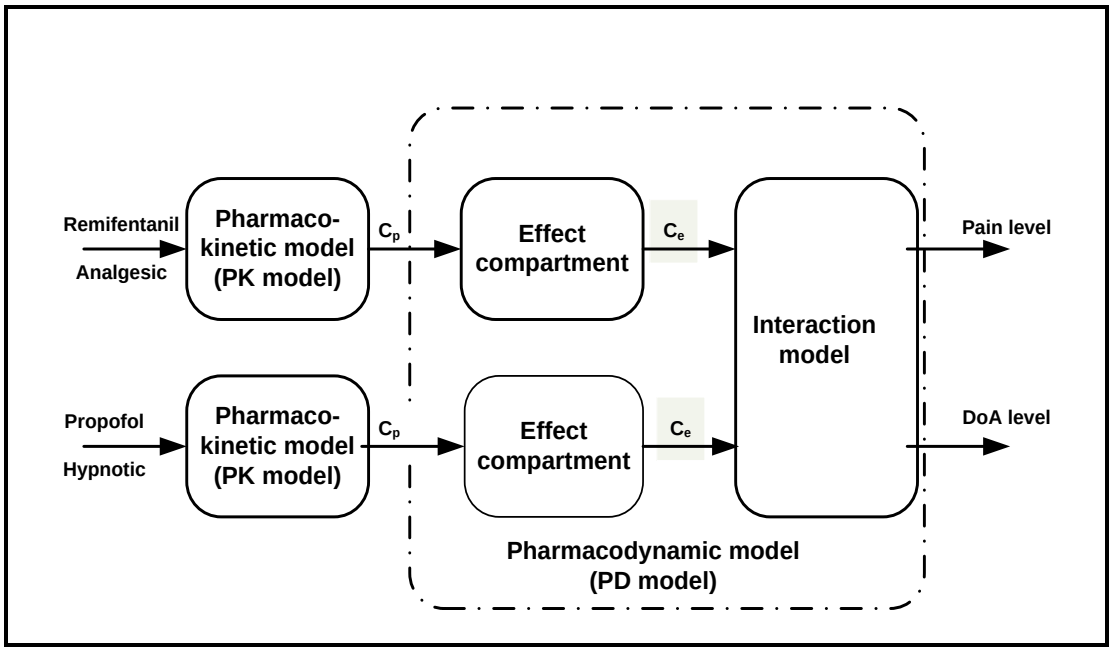

Figure 4.1: Depth of anaesthesia model for internal model control

The PK model provides the Propofol plasma concentration from a given dose of Propofol injected into the patient, as it can be seen in Figure 4.2. A three-compartment model is used, in which the main compartment represents intravascular blood (blood within arteries and veins) and highly irrigated organs (such as heart, brain, liver and kidney). The other two compartments represent muscles, fat, and other organs or tissues (Volyanskyy, Haddad & Bailey 2009).

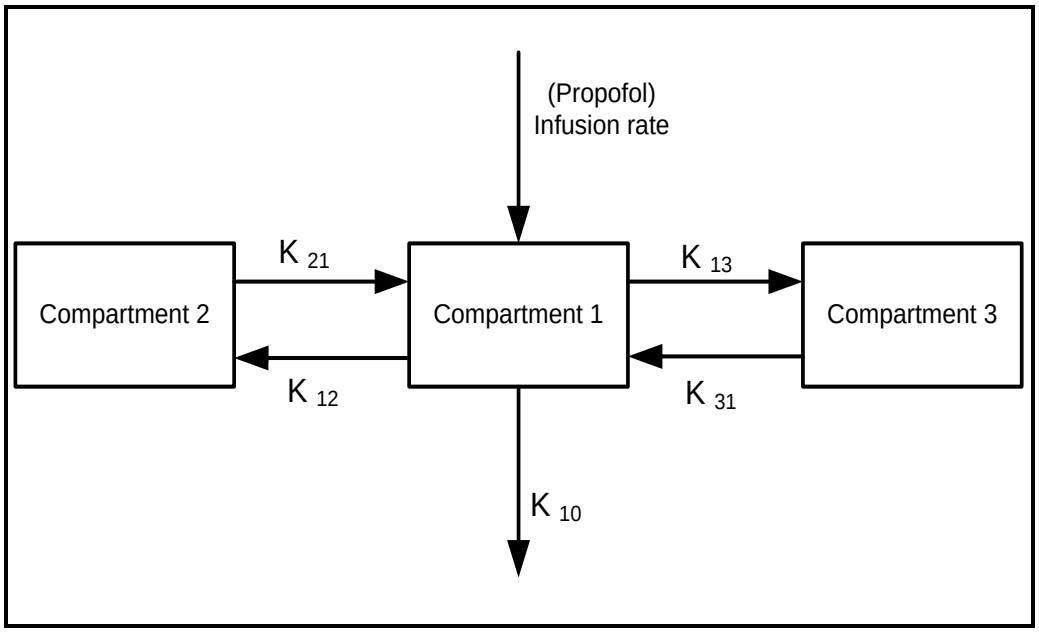

Figure 4.2: Pharmacokinetic compartments model

$$\begin{cases} \dot{x_1} = A_1 x_1 + B_1 u \\ c_p^{prop} = C_1 x_1 \end{cases} \tag{4.1}$$

with $A_1 = \begin{bmatrix} -k_{10} - k_{12} - k_{13} & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{bmatrix}$

$B_1 = \begin{bmatrix} \frac{10^4}{3600} \\ 0 \\ 0 \end{bmatrix}$, $C_1 = \begin{bmatrix} \frac{1}{1000 \times v_1} & 0 & 0 \end{bmatrix}$ and

$v_1 = \text{weight} \times v_c$

where v_1 is measured with the weight of the patient and coefficient v_c [L/kg] which represents the volume of compartment one per patient unit weight [kg] (Gentilini, et al. 2001).

A pharmacodynamic model presented as a low-pass filter is used to relate the Propofol plasma concentration c_p^{prop} and the Propofol effect concentration c_e^{prop}. This yields the following state space representation (Niño et al. 2009):

$$\begin{cases} \dot{x_2} = A_2 x_2 + B_2 c_p^{prop} \\ c_e^{prop} = C_2 x_2 \end{cases} \tag{4.2}$$

where $A_2 = -K_{e0}, B_2 = -K_{e0}$ *and* $C_2 = 1$.

The effect-site concentration is related to DoA as Hill equation (Munson & Bowers 1967):

$$E(t) = E_o - E_{max} \frac{{C_e}^{\gamma}}{EC_{50}^{\gamma} + {C_e}^{\gamma}} \tag{4.3}$$

where C_e is:

$$C_e(s) = \frac{k_{e0}}{s + k_{e0}} C_p(s) \tag{4.4}$$

where k_{e0} is the inverse of the effect-site compartment time constant and EC_{50} is the half-maximal effective concentration.

The mathematical model employed in this study on hypnosis and analgesia control is a combination of a linear PK model and a nonlinear PD model. The PK model parameters can be approximately estimated through covariate adjustments of weight, age and sex, but it is not possible to estimate the PD parameters. The designed controller should be robust and result in stable responses for all patients characterized by a range of PD parameters. From a clinical point of view, a perfect controller would lead the induction of anaesthesia in order to achieve the goal as fast as possible without initial overshoot. After that, the controller would simply keep up the desired target as well as possible.

4.3 Controller Design and Implementation

The internal model control principle states that a plant or a process can be controlled only if the control system incorporates or encapsulates, either implicitly or explicitly, some representation of the process (Lee, Morari & Garcia 1994). For example in an open loop control, the model of the process to be controlled is almost exactly known (Kaya 2004). However, an exact model of the plant is not known in almost all practical cases and process-model mismatch is very common. These uncertainties and un-modelled dynamics in the system usually affect system performance. In such cases Internal Model Control (IMC) is found to be very useful (Tan, Marquez & Chen 2003; Yelneedi, Samavedham & Rangaiah 2009).

The disadvantage of the linear IMC controller is that it cannot handle open-loop unstable systems and nonlinear models should be linearized for the controller design as shown in Figure 4.3. where $G_c(s)$ is the controller and it is used to control the

process, $G_p(s)$. Assuming $\widetilde{G_p}(s)$ is a model of $G_p(s)$. The inverse of the model of the process is equal to $G_c(s)$,

$$G_c(s) = \widetilde{G_p}(s)^{-1} \tag{4.5}$$

And if $G_p(s) = \widetilde{G_p}(s)$, this means the model is an exact representation of the process. Then it is obvious that the setpoint and the output will always be equal.

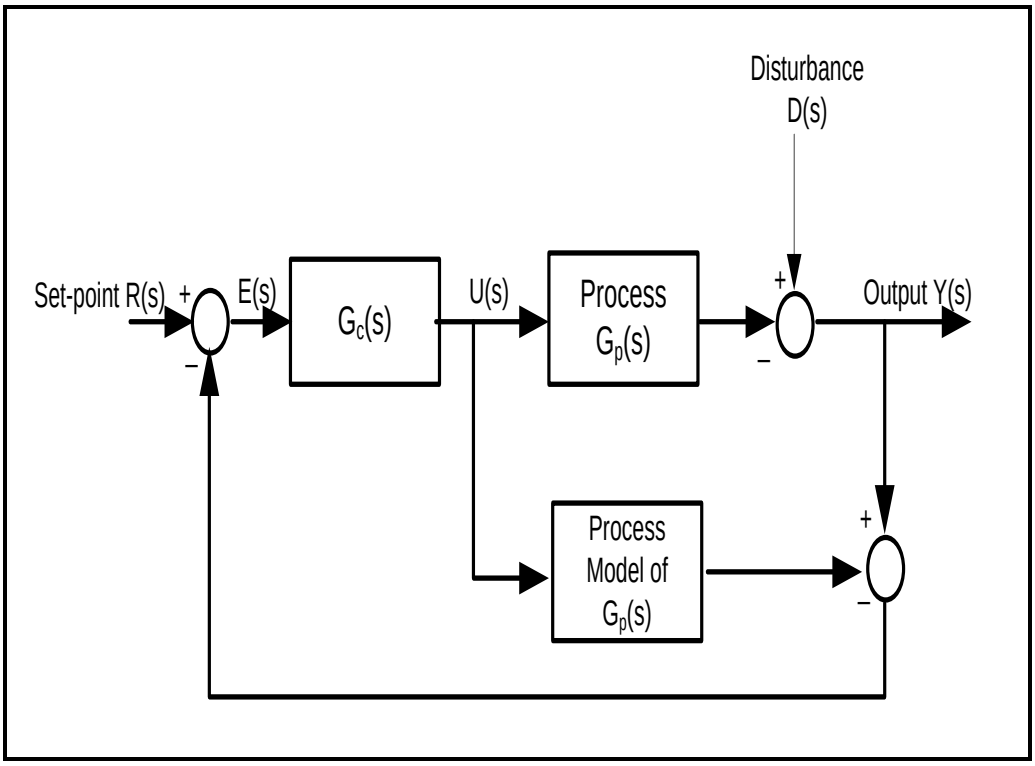

Figure 4.3: Block diagram of the Internal Model Control

This means that we must have complete knowledge about the process under control with perfect control performance. This also means that the feedback control is necessary only when information about the process is incomplete and imprecise. As process-model mismatch is common, that means the invertible of the process may be

complicated and as a result the system is often affected by noises and unknown disturbances. The disturbance affecting the system is D(s) in Figure 4.3. The planning input U(s) is introduced together with the model and the process (Yelneedi, Samavedham & Rangaiah 2009). The difference between the process output Y(s), and the output of the model is the signal $\widetilde{\mathrm{D}}(\mathrm{s})$. The $\widetilde{\mathrm{D}}(\mathrm{s})$ can be found as:

$$\widetilde{\mathrm{D}}(\mathrm{s}) = \{\mathrm{G_p}(\mathrm{s}) - \widetilde{\mathrm{G_p}}(\mathrm{s})\}\mathrm{U}(\mathrm{s}) + \mathrm{D}(\mathrm{s}) \tag{4.6}$$

From equation 4.6, if D(s) is equal to zero, then $\widetilde{\mathrm{D}}(\mathrm{s})$ is the measure of the difference in behaviour between the process and its model. Also if $\mathrm{G_p}(\mathrm{s}) = \widetilde{\mathrm{G_p}}(\mathrm{s})$, that means $\widetilde{\mathrm{G_p}}(\mathrm{s})$ is equal to the unknown disturbance or noise. As a result $\widetilde{\mathrm{D}}(\mathrm{s})$ is regarded as the information that is missing in the model, $\widetilde{\mathrm{G_p}}(\mathrm{s})$, and can be used to improve control. The control signal can be written as,

$$\mathrm{U}(\mathrm{s}) = \left[\mathrm{R}(\mathrm{s}) - \widetilde{\mathrm{D}}(\mathrm{s})\right] \mathrm{G_c}(\mathrm{s}) =$$

$$\left\{\mathrm{R}(\mathrm{s}) - \left[\mathrm{G_p}(\mathrm{s}) - \widetilde{\mathrm{G_p}}(\mathrm{s})\right]\mathrm{U}(\mathrm{s}) - \mathrm{D}(\mathrm{s})\right\} \mathrm{G_c}(\mathrm{s}) \tag{4.7}$$

Because $\mathrm{Y}(\mathrm{s}) = \mathrm{G_p}(\mathrm{s})\mathrm{U}(\mathrm{s}) + \mathrm{D}(\mathrm{s})$ then the closed loop transfer function for IMC is equal to:

$$\mathrm{Y}(\mathrm{s}) = \frac{[R(s) - D(s)]\, G_c(s) G_p(s)}{1 + \left[\mathrm{G_p}(\mathrm{s}) - \widetilde{\mathrm{G_p}}(\mathrm{s})\right]\mathrm{G_c}(\mathrm{s})} + \mathrm{D}(\mathrm{s}) \tag{4.8}$$

From the equation 4.8, we can see that, if $\mathrm{G_c}(\mathrm{s}) = \widetilde{\mathrm{G_p}}(\mathrm{s})^{-1}$ and if $\mathrm{G_p}(\mathrm{s}) = \widetilde{\mathrm{G_p}}(\mathrm{s})$, that means perfect setpoint tracking and disturbance rejection is accomplished. Also

we can see that, theoretically, if $G_p(s) \neq \widetilde{G_p}(s)$, perfect setpoint tracking and disturbance rejection can still be realised provided $G_c(s) = \widetilde{G_p}(s)^{-1}$. Furthermore, to advance robustness, the process model mismatch and its effects should be minimised. Because a distinct difference and failure to match between process and model performance usually occur at the high frequency end of the system's frequency response, a low pass filter $G_f(s)$ is usually added to attenuate the effects of process and model discrepancies (Linkens & Mahfouf 2000). As a result, the internal model controller is usually designed as the inverse of the process model in the series with a low-pass filter.

The structure of the RIMC in DoA is depicted in Figure 4.4. The blocks PK and PD, together with the nonlinear equation, represent the patient's pharmacokinetics and pharmacodynamics, respectively. Both PK and PD are single-input single-output linear time invariant (LTI) systems. The equivalent parallel models for the pharmacokinetics and pharmacodynamics are represented by $\widetilde{PK}$ and $\widetilde{PD}$ respectively together with linearization constant K.

where $K = -\frac{BIS_0 \gamma}{4EC_{50}}$

In Figure 4.4, the controller G_c regulates the BIS by adjusting the input (infusion rate) of the Propofol based on the difference between set point and the actual BIS. A saturated block is added after the controller G_c to keep the input within the constraints specified. Because the controller G_c is the filtered inverse of the nominal patient model, the tuning of the RIMC depends on the filter time constant, λ and order of the filter, n. By adjusting this filter time constant, we can handle inter-

patient variability for each patient for robustness and for speed response (Brosilow & Joseph 2002).

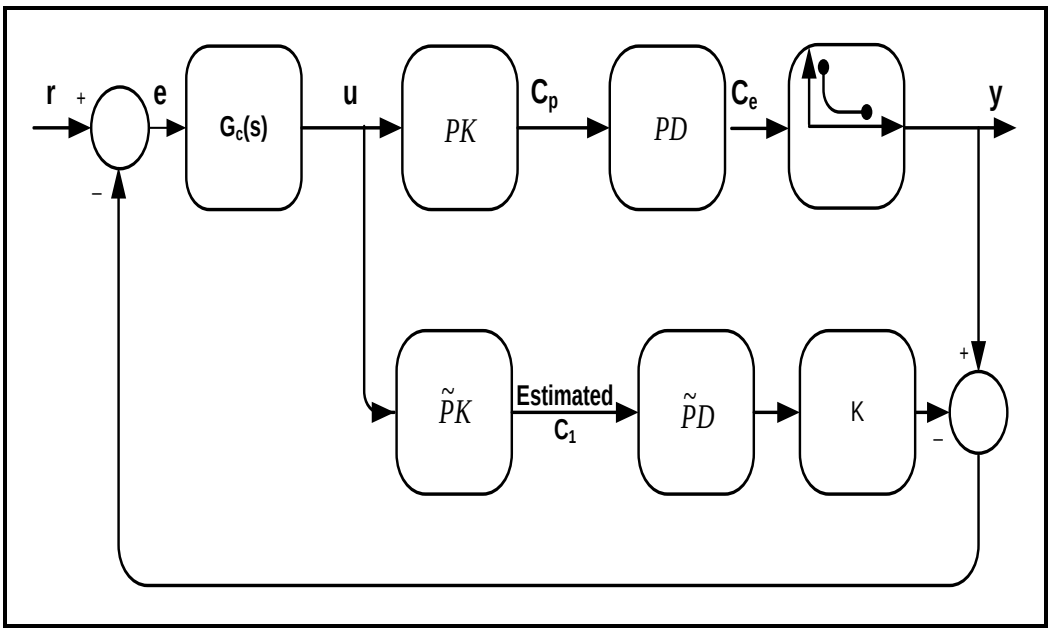

Figure 4.4: Block diagram of the IMC structure

4.4 Simulation and Results

The data from hospitals is recorded into a Matlab spreadsheet. In the case of hardcopy form, the data is manually entered into the Matlab spreadsheet. These data are collected and analysed to establish the relative importance of each independent variable in the prediction. The data analysis results are integrated for model development. The models are developed and designed based on this data analysis, and initial results are presented. Then simulations are carried out to study the feasibility and reliability. Testing is scheduled to the final stage of model development. In this study, however, the IMC is used to generate and provide a much easier framework for the design of robust control systems.

The proposed control schemes were implemented and tested in simulation using Simulink. The nonlinear DoA model is shown in the block diagram in Figure 4.5. To perform these actions, a Matlab program was developed to compute parameters for

both linear and nonlinear Simulink models. The Matlab programs were developed to evaluate the influence of several parameters (γ, K_{eo}, and c_e^{prop}) on the nonlinear model. The simulations evaluate the influence of drugs in steady state on the Hill equation. The BIS and the infusion rate in typical cases are shown.

Figure 4.6 shows the closed loop implementation in Simulink for controlled output (BIS) using RIMC. The controller performance over the family of the patients is affected due to inter-patient variability, when using a nominal model for RIMC strategy. Notice that the IMC strategy includes an identification of the patient specific parameters, and therefore, takes into account the patient variability to obtain a better control performance.

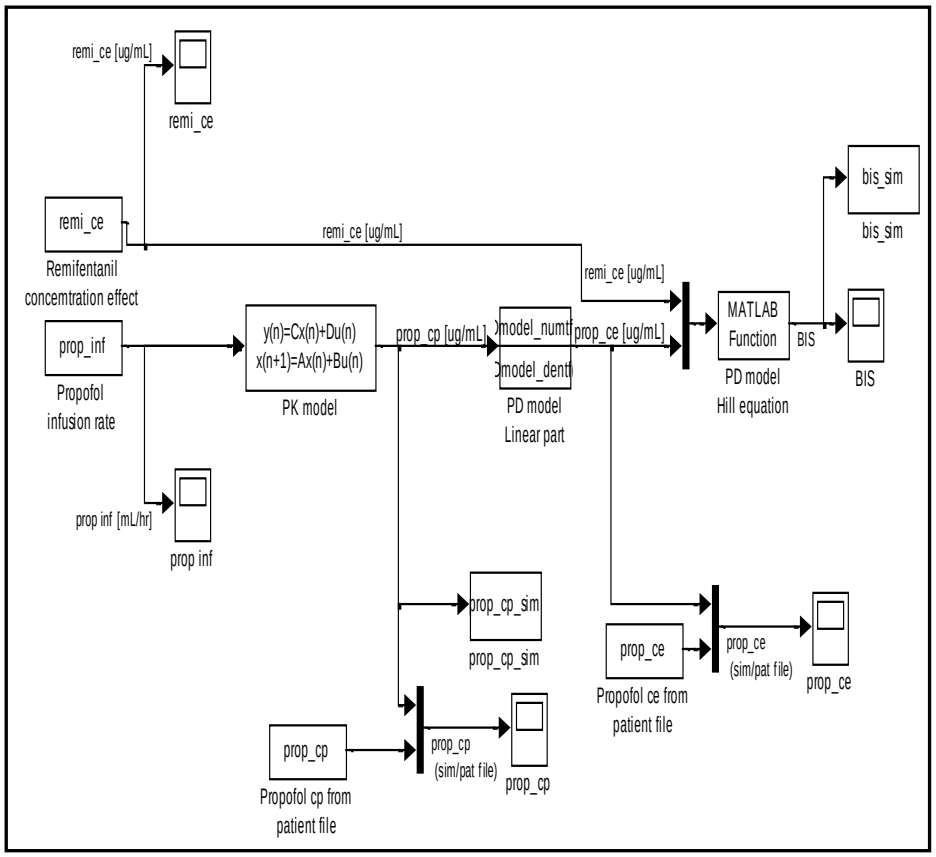

Figure 4.5: The block diagram of DoA model built in Simulink

The proposed algorithm is simulated using the patient's parameters (in Table 4.1) for all 15 patients model (the infusion and the drug effect are represented by the PK and PD models), and the amount of the drug is varied between 3 and 7 μg/ml for the target (BIS =40). The observed time to target in seconds is required for reaching first time the target interval of (between 45, 55) BIS values. Because of plasma Propofol concentration measurement is unavailable, it is estimated through the nominal PK model. BIS is measured online. The controller has maintained BIS between 40 and 60 during the period of surgery. First, it is assumed that the patient is in a fully awake state (BIS≈100) and then the controller is turned on, and the set point is changed manually from 100 to 50. Set point changes are often made in the variables during the operation depending on the surgical procedure being performed. The controller should perfectly respond to these changes without any considerable delay in the response. This condition brings the patient to the surgical operating range (40 ≤ BIS ≤60) which must be maintained for the period of the surgery.

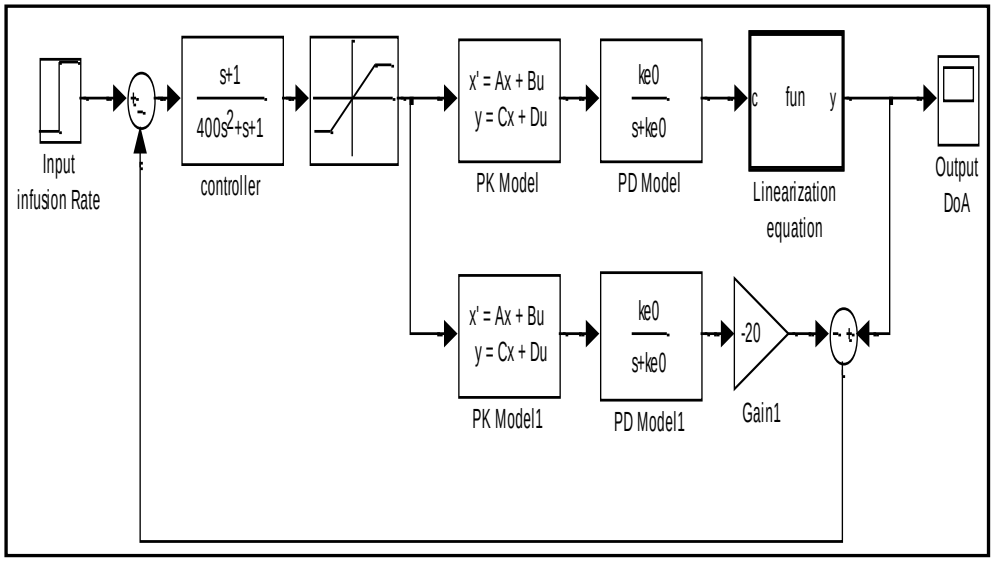

Figure 4.6: Non-linear DoA model built in Simulink

Table 4.1: Values of the parameters for the 15 patients Sets arranged in the decreasing order of their BIS sensitivity to Propofol infusion

Parameter								
Patient no.	k_{10}	k_{12}	k_{21}	k_{13}	k_{31}	k_{e0}	EC_{50}	γ
1 (sensitive)	0.08925	0.084	0.06875	0.031425	0.004125	0.459	1.6	2
2	0.14875	0.14	0.04125	0.052375	0.004125	0.239	1.6	2
3	0.14875	0.112	0.04125	0.0419	0.004125	0.239	1.6	3.133
4	0.14875	0.14	0.04125	0.052375	0.004125	0.239	1.6	3.133
5	0.08925	0.084	0.04125	0.052375	0.002475	0.459	2.65	2.551
6	08925	0.084	0.06875	0.031425	0.002475	0.349	2.65	2.551
7	0.14875	0.112	0.06875	0.031425	0.002475	0.459	2.65	2.551
8 (nominal)	0.119	0.112	0.055	0.0419	0.0033	0.349	2.65	2.551
9	0.119	0.112	0.055	0.0419	0.0033	0.239	2.65	2
10	0.119	0.112	0.055	0.0419	0.0033	0.239	2.65	2.551
11	0.08925	0.084	0.06875	0.031425	0.002475	0.459	3.7	2
12	0.14875	0.112	0.06875	0.031425	0.002475	0.349	3.7	2.551
13	0.08925	0.084	0.06875	0.031425	0.002475	0.239	3.7	2.551
14	0.08925	0.084	0.06875	0.031425	0.002475	0.239	3.7	3.133
15 (insensitive)	0.08925	0.084	0.04125	0.052375	0.002475	0.239	3.7	3.133

The predicted plasma Propofol concentration must be among 1 μg/mL and 5 μg/mL. The lower bound guarantees a lowest amount delivery of anaesthetic, whereas the upper bound prevents overdosing of the drug for an average subject. The manipulated variable (Propofol infusion rate) u is constrained between 0 and 40 mg/kg/h. The higher bound is needed because higher Propofol infusion leads to a rapid increase of Propofol concentration in the subject's body and this may lead to hypnotic crisis, cardiac arrhythmia, or even cardiac arrest. The lowest amount bound on u reflects the impossibility of administering negative concentrations of Propofol.

Because the safe regulation of the DoA level is crucial during the surgery, the constraints imposed on the inputs are hard constraints. That is, at any time the controller should not violate these limits. The modification parameters for the RIMC controller are the filter time constant λ , which is set at 1.7 and the order of the filter n which is set at 2. Here also, the value of K used is -24.16. For the PID controller, the tuning of the three parameters (K_c , τ_I and τ_D) is required to get faster response of BIS without any offset or oscillations. Here, the PID parameters are obtained using the optimization toolbox of Matlab to get the best performance with this control structure. With the PID controller, the settings were $K_c = -0.06, \tau_I = 28.5$, and $\tau_D = 2.4$.

During the induction phase, (the control execution interval is set between 5 and 10 seconds, which is the sampling interval for BIS), the IMC strategy is relatively high performing. The IMC controller brings the BIS variable to the reference interval; the input variable (drug infusion rate) is restricted between 0 to 40 mg/kg /h. The results in this study can be attributed to the fact that the RIMC controller is a more cautious

controller, giving an exchange among small time-to-target, small undershoot and robustness against patient variability as shown in Figure 4.7.

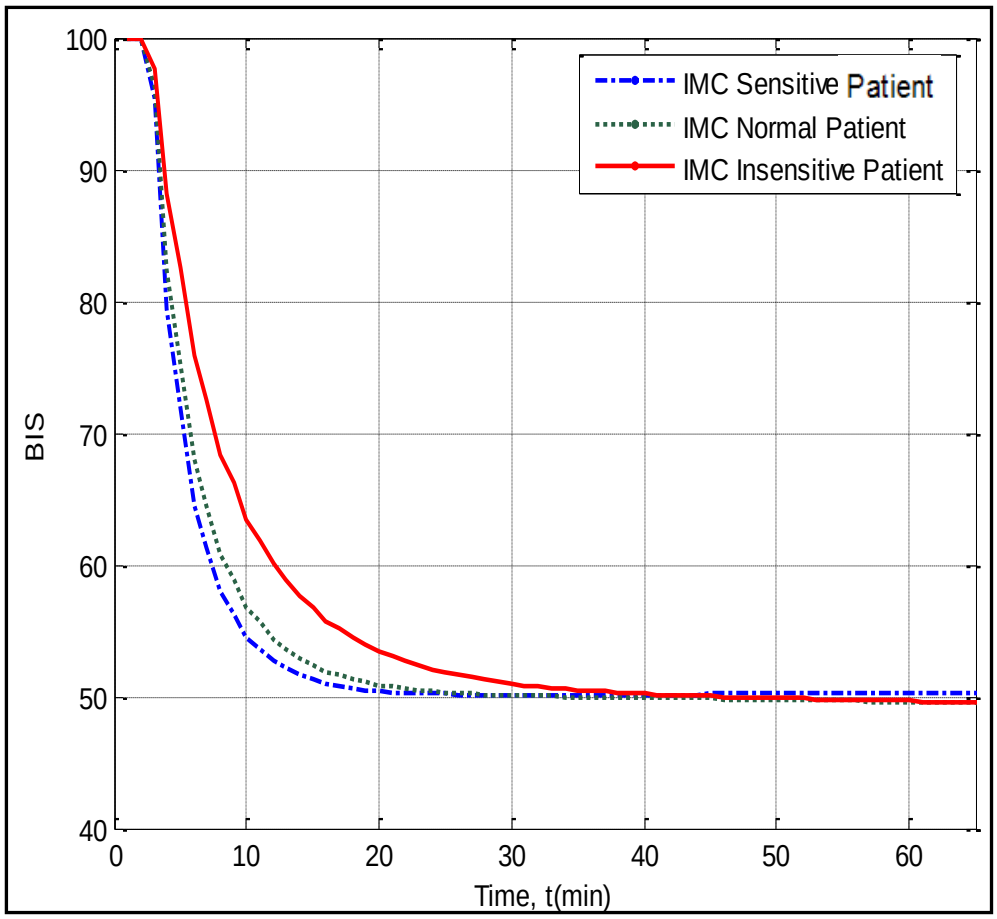

Figure 4.7: Performance of the IMC controller

The response of a PID controlled system is faster than that of the IMC controller, and a small offset persists throughout the simulation time. Figure 4.8 shows the predicted plasma Propofol concentration, where it is seen that both controllers result in overshoot (higher with PID controller) but are still maintained within the constraints. The results of this study indicate that the two controllers are able to meet performance specifications despite significant and reasonable variation in the model parameters (inter- patient and intra-patient variability) as shown in Table 4.1. At this

point, we assume that variability in both the PK and PD is depending on the patient's model parameters and on the patient's sensitivity to the drug.

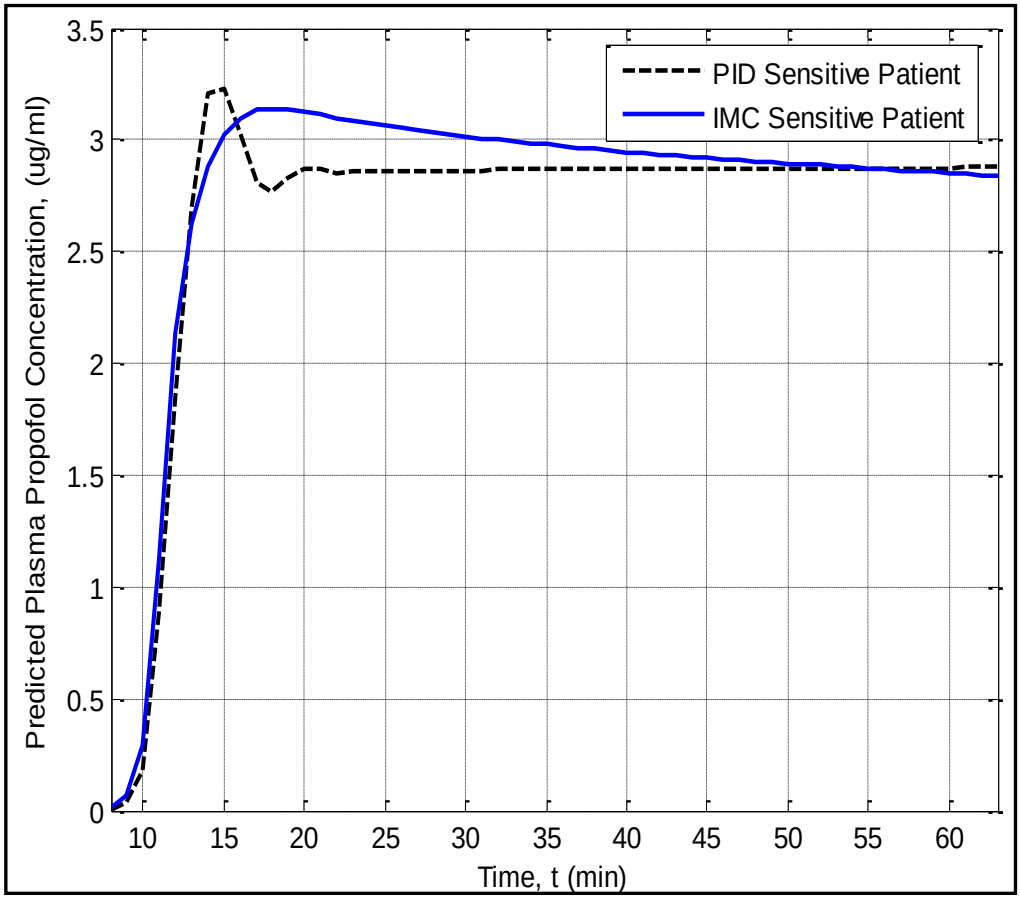

Figure 4.8: Performance of the PID controller

The current study found that the variability in PD parameters has a higher impact on BIS than the variability in PK parameters. First, each (k_{10}, k_{12}, k_{21}, k_{13}, k_{31}, V_1, V_2, and V_3) PK parameter is assumed to be different over three levels, from a minimum, to average, and then to a maximum. Simulations showed that changes in volumes of the three compartments (V_1, V_2, and V_3) has a very small amount effect on the performance. For the insensitive patient, running down rate constants of the central compartment (k_{10}, k_{12}, and k_{13}) are high (0.148, 0.139, and 0.05211, respectively) and generating rate constants (k_{21}, k_{31}) are low (0.042, and 0.00219, respectively) as shown in Figure 4.9 and Figure 4.10.

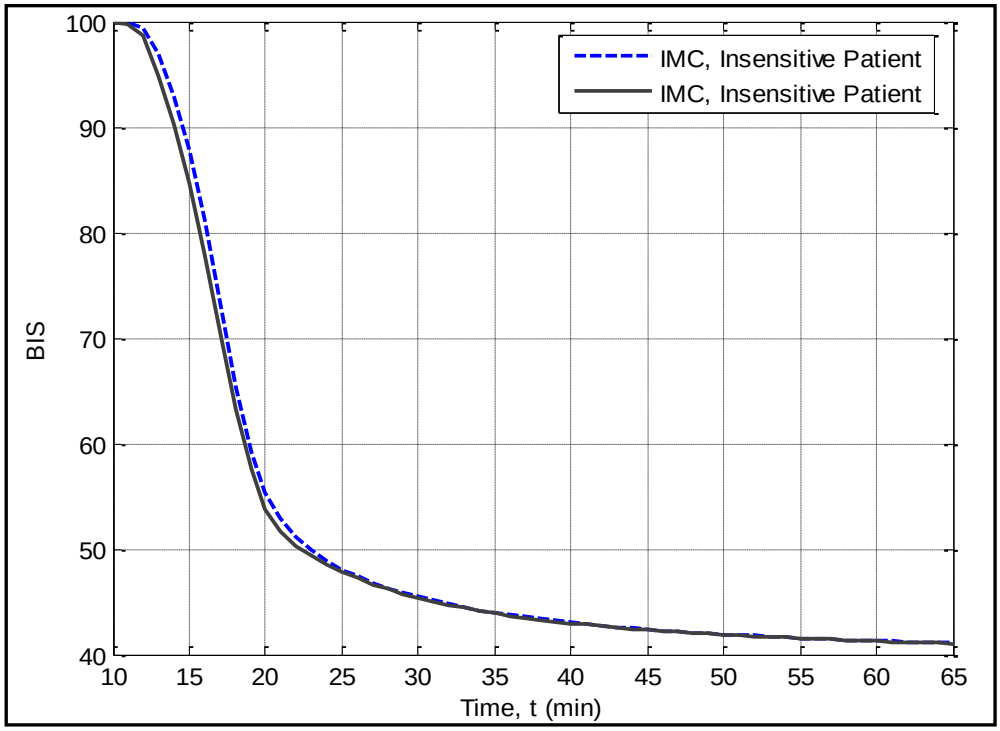

Figure 4.9: Performance of the IMC for two insensitive patients

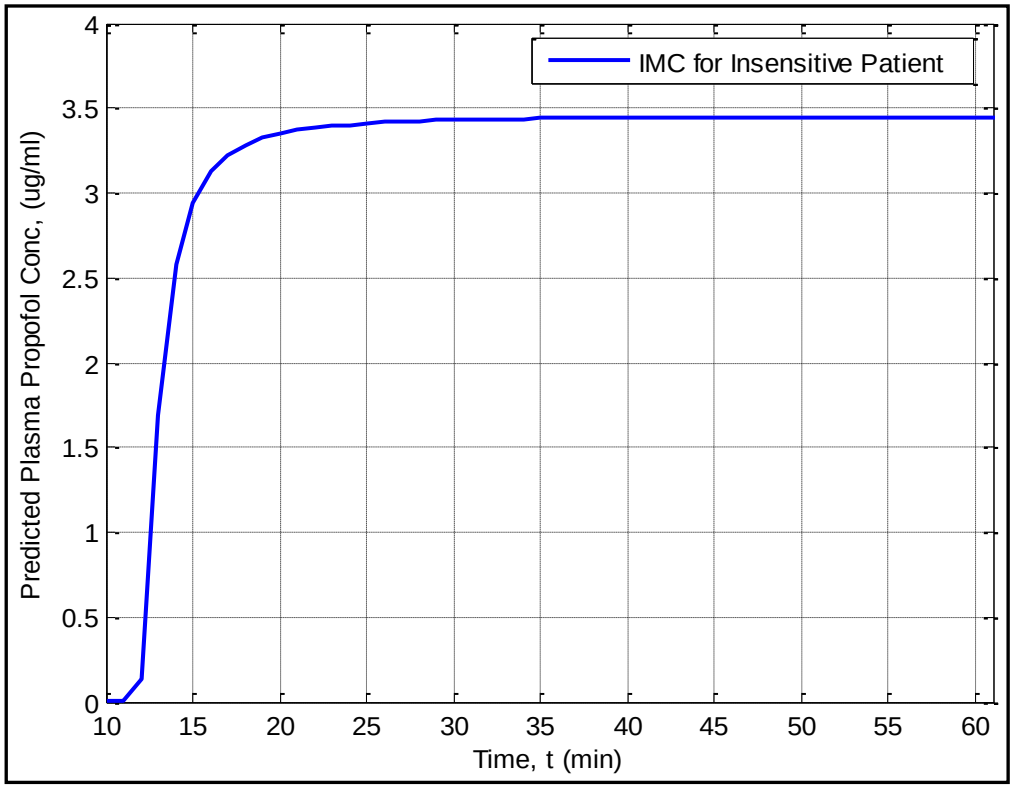

Figure 4.10: Performance of the IMC for different patient

In the PD parameters, higher EC_{50} (3.6) indicates the need for more drug to obtain the same DoA level, higher γ (3.1119) represents higher nonlinearity and lower k_{e0} (0.2388) indicates sluggishness in response as can be seen from the Figure 4.11 and Figure 4.12.

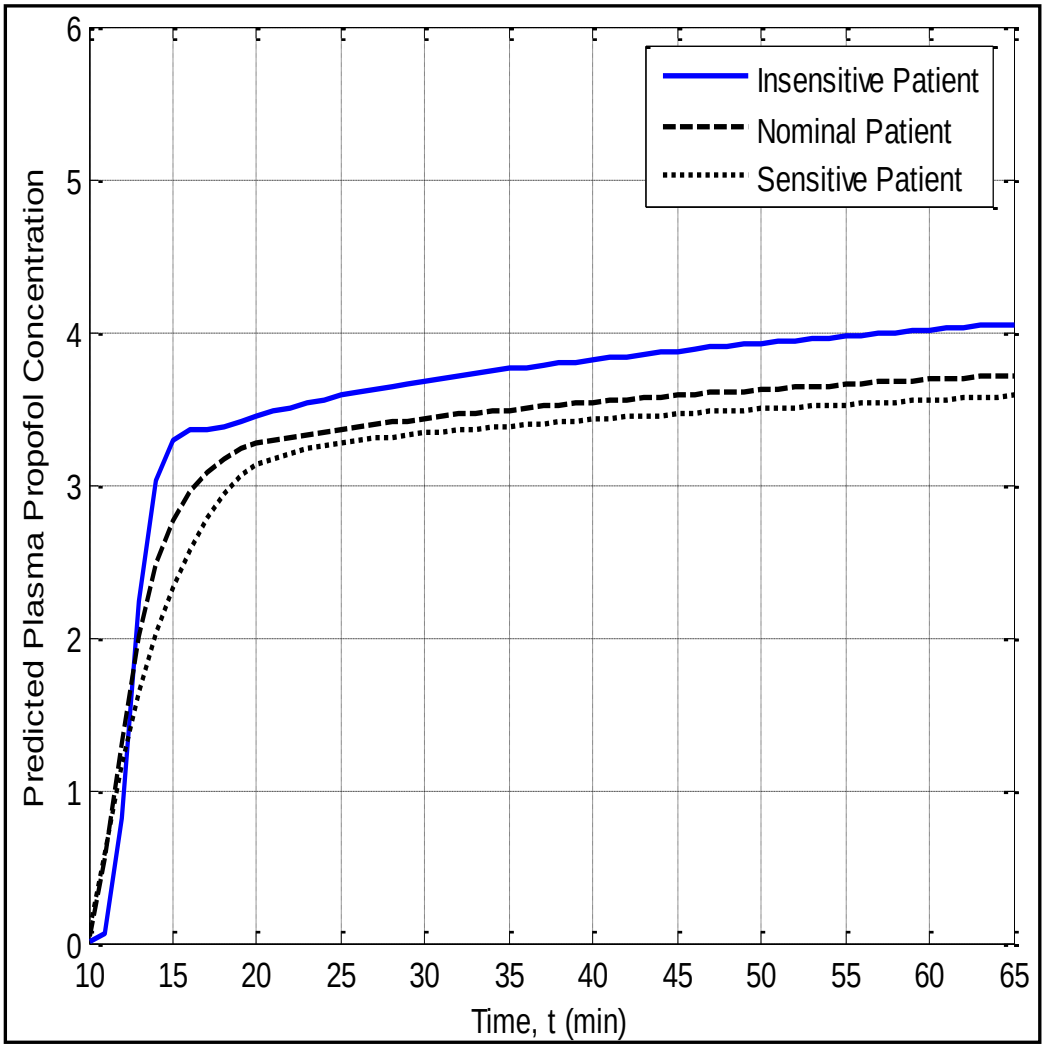

Figure 4.11: Performance of the PID for different patients

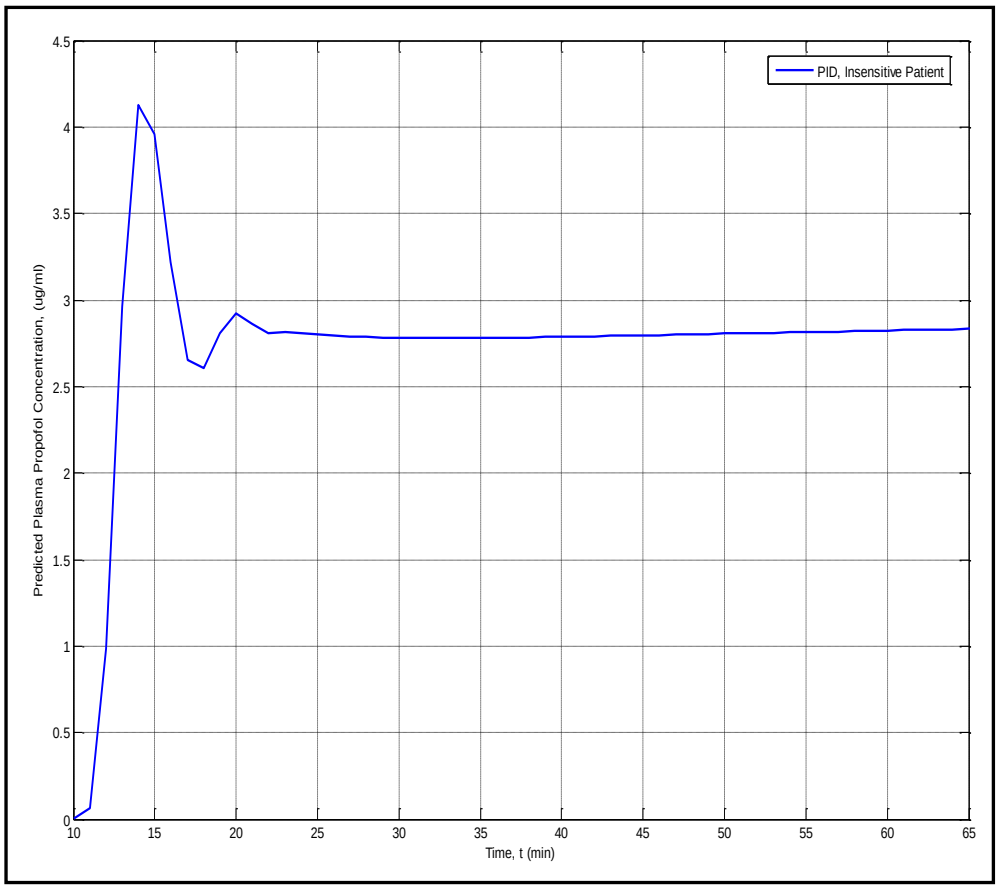

Figure 4.12: Performance of the PID for two insensitive patients

For the sensitive patient, k_{10}, k_{12}, and k_{13} are low (0.09, 0.0839, and 0.0321, respectively) and k_{21}, k_{31}, are high (0.0691, and 0.0039, respectively). In the PD parameters, lower EC_{50} (1.6) indicates the need for a smaller amount of drug to obtain the same DoA level, lower γ (2) represents lower nonlinearity, and higher k_{e0} (0.459) indicates more rapid responses. Furthermore, since k_{e0} represents the process gain, higher k_{e0} (higher gain) represents a faster response and lower k_{e0} (lower gain) represents a slower response of the process. This can be seen from the Figure 4.13, Figure 4.14 and Figure 4.15(Niño et al. 2009).

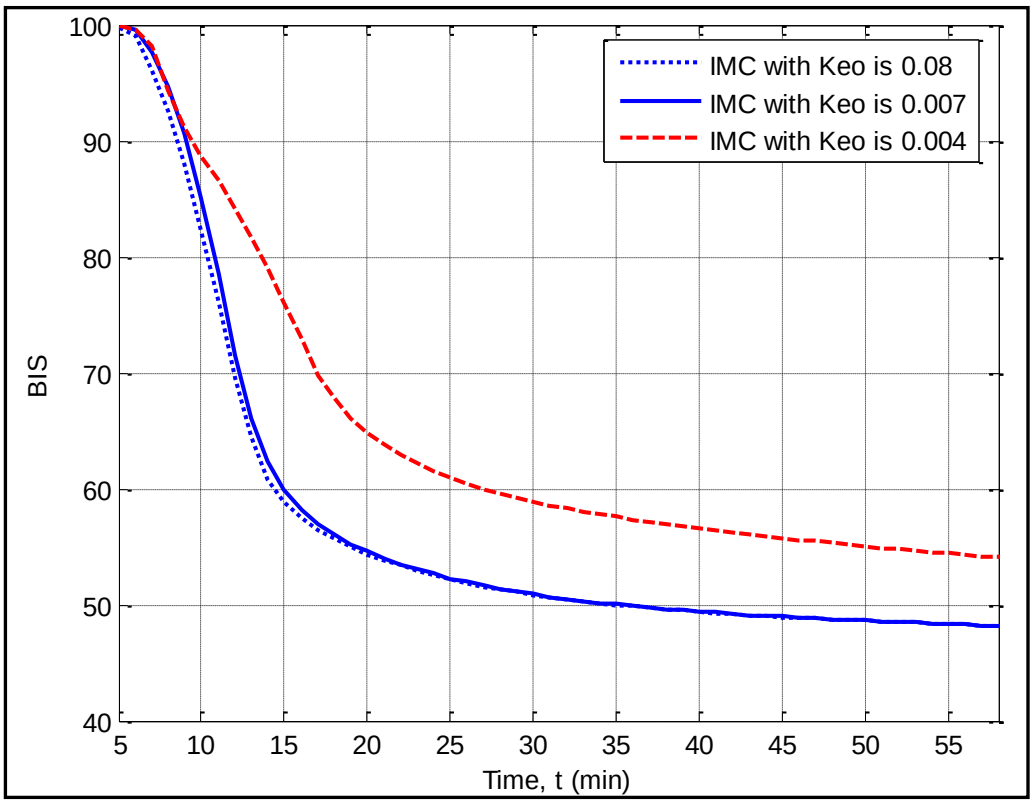

Figure 4.13: Parameters influence on the DoA and on k_{e0}

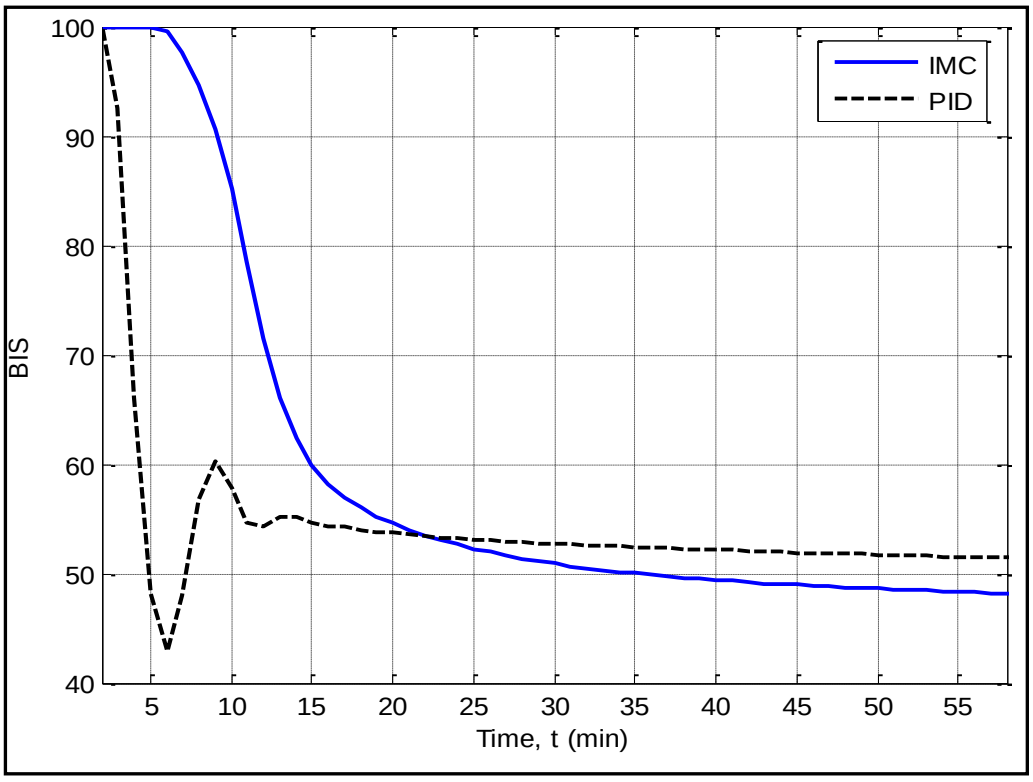

Figure 4.14: Performance of the IMC and PID controller

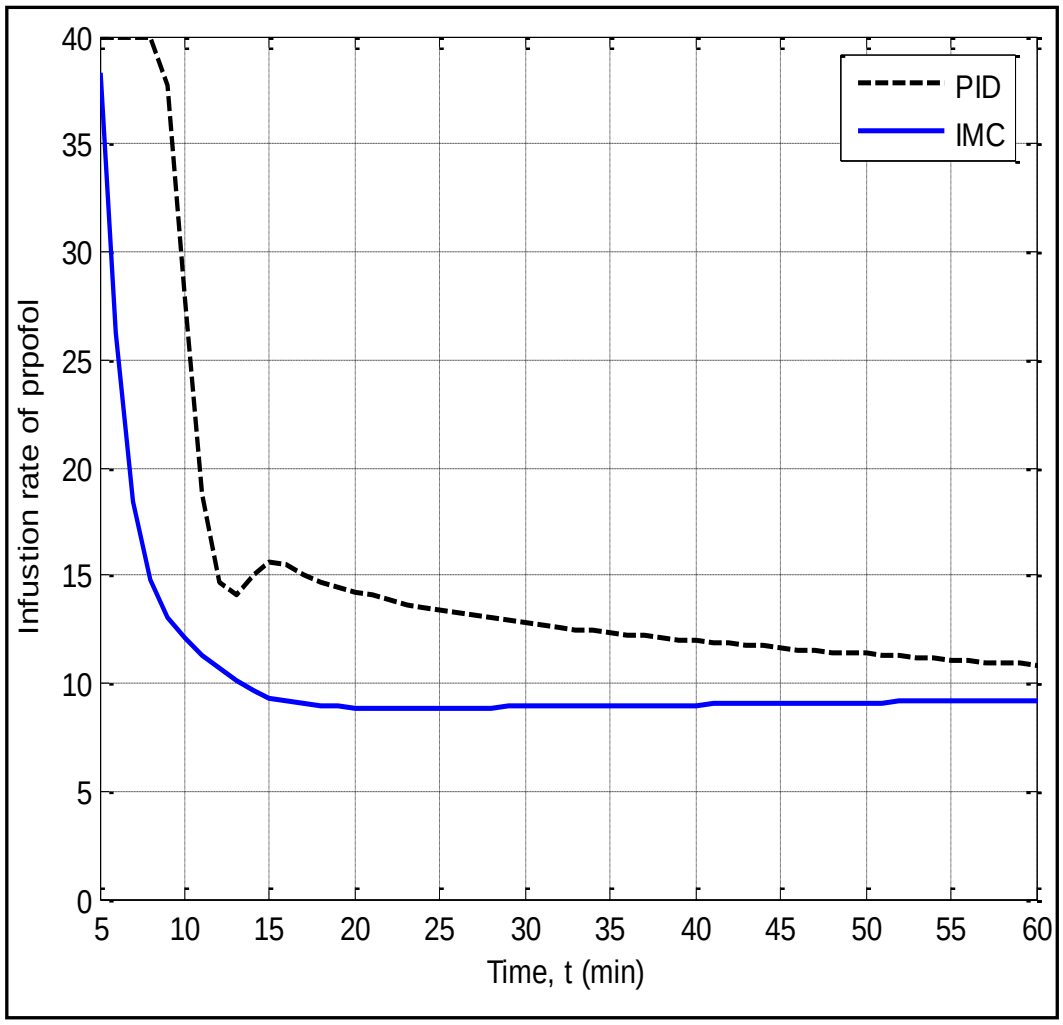

Figure 4.15: Performance of the IMC and PID controller

It can be noticed that γ and c_{50E}^{prop} influence the DoA contrary to $c_{50E}{}^{remi}$ which the effect on the output is negligible. Concerning the linear part, the gain has an influence on the DoA signal comparable to the ones of γ and c_{50E}^{prop} . The effect of the k_{e0} is negligible on both DoA and c_p^{prop} signals based on these simulation results.

4.5 Conclusions

In this study, a robust internal model control, for regulation of anaesthesia using BIS as the controlled variable, has been developed and evaluated thoroughly. The performance of this controller is considered along with the performance of the traditional PID controller. In comparison with traditional PID controller, the proposed robust internal model control is found to be robust to intra- and inter-patient variability, and better at handling disturbances and measurement noise. In system performance, the settling time has been shortened ($\cong 5$ min) and the performance had no undershoot in the RIMC. Undershoot was higher with PID controller. The performance of the IMC controller is found to be better and hence, it is recommended for DoA control. The proposed RIMC strategy was also found to be more robust to intra- and inter-patient variability.

CHAPTER 5

SMITH PREDICTIVE CONTROL FOR PATIENT MODEL WITH TIME-DELAY

5.1 Human Body Model for Depth of Anaesthesia Control

Advanced control methodologies have been and are being extensively developed for highly complex engineering systems. Specifically, robust control systems have been developed that ensure system stability and performance in the expression of system modeling uncertainty, system disturbances, and system nonlinearities. However, modern control technology has received far less consideration in medical control systems such as depth of anaesthesia control. One of the main reasons is the steep barriers to communication between mathematics/control engineering and medicine. However, this is slowly changing and there is no doubt that control-system technology has a great deal to offer medicine. This is particularly true when dealing with critically ill patients in the intensive care unit or in the operating room. These

patients often require the administration of drugs to regulate key physiological variables, such as level of consciousness, heart rate, blood pressure, ventilator drive, etc., within desired targets (Sreenivas et al. 2009). The rate of administration of these drugs is critical, requiring constant monitoring and frequent adjustments. Open-loop control (manual control) by clinical personnel can be tedious, imprecise, time-consuming, and sometimes of poor quality. Hence, the need for closed-loop control in medical systems is significant, with the potential for improving the quality of medical care as well as curtailing the increasing cost of health care.

During anaesthesia, there is a time-delay between the administration of the drug and the start of mixing in the central nerve system, estimation of the time-delay is an important issue in surgery (Gentilini et al. 2001; Zanner et al. 2009). The pharmacokinetic time-delay is consistent for each individual patient, but can vary significantly between different patients. Researchers found that intra-patient parametric uncertainty reaches 30 % at most for the PK time delay, while inter-patient uncertainty can be as high as 70 % (Bibian 2006). Similar results were found for the overall pharmacokinetic-pharmacodynamic gain (Dumont, Martinez & Ansermino 2009; Yue & Han 2005). The origin of the time-delay is the period from the start of infusion pump until the drug is distributed along the central nerve system; the TD varies from one time instant to another, dependent on the signal quality. If not dealt with appropriately, such varying TD are a source of poor feedback control in the medicine system (Kaya 2004; Robayo et al. 2010).

For this study, the open loop transfer function is followed by a time delay modeled using a 1^{st} order Pade approximation. The structure of the Pade

approximation enables an effective reconstruction of a function's singularities over the whole range using its series expansion obtained for small values of its variable (Lucchese & McKoy 1983).

The aim of this chapter is to establish and validate a TD estimation method using Smith Predictive Control (SPC) to overcome the lack of TD information for closed-loop sedation in surgery. This study addresses two types of time-delays, instrumentation and non-instrumentation time-delay during anaesthesia induction and the effect of that time-delay on DoA system responses. This study investigated the situations with and without time-delays. The results show that the proposed scheme has reduced system response overshoot and undershoot by about 15%, and reduced the settling times by about one to two minutes.

The patient's body is divided into several compartments to drive the pharmacokinetic model (Sreenivas, Lakshminarayanan & Rangaiah 2007). In each compartment, the drug concentration is homogeneous as shown in Figure 4.2. The most common hypnotic drug is propofol that used in general anaesthesia. The distribution of this drug in the body can be described by pharmacokinetic and pharmacodynamic models (Van Poucke, Bravo & Shafer 2004; Volyanskyy, Haddad & Bailey 2009). The BIS ranges between 0 and 100 and it is related to the effect of the hypnotic drug by a nonlinear relation called the Hill curve (Nunes et al. 2005; Sreenivas, Lakshminarayanan & Rangaiah 2007). Zero means that the patient does not have cerebral activity and a 100 denotes full consciousness. The PK model provides the Propofol plasma concentration from a given dose of Propofol injected to the patient.

PK model is expressed as:

$$PK(s) = \frac{C_p(s)}{u(s)} = \frac{A}{(s + p_1)} + \frac{B}{(s + p_2)} + \frac{C}{(s + p_3)} \quad (5.1)$$

where $C_p(s)$ is the drug concentration expressed in microgram per milliliter (Propofol), p_1 and p_2 in the above formula would refer to the rate constant of the distribution phase, and p_3 is the rate constant of the elimination phase.

$u(s)$ is the control input.

PD is expressed as:

$$PD(s) = \frac{k_{e0}}{(s + k_{e0})} + \frac{\gamma}{4EC_{50}} \quad (5.2)$$

where k_{e0} is the inverse of the effect-site compartment time constant and EC_{50} is the half-maximal effective concentration.

The Hill curve is represented by the following equation:

$$BIS(t) = E_0 - E_{max} \cdot \frac{{C_e}^{\gamma}(t)}{{C_e}^{\gamma}(t) - {C_{50}}^{\gamma}} \quad (5.3)$$

E_0 denotes the baseline value (awake state) and by convention a value of 100 is assigned. E_{max} denotes the maximum effect achieved by the drug. Ce is the drug effect-site concentration, EC_{50} is the drug concentration at half-maximum effect and

represents the patient's sensitivity to the drug, and γ determines the steepness of the curve.

The patient's PK and PD models are used to predict the BIS output as a result of drug infusion. The generalized PK-PD model for Propofol is shown in Figure 5.1.

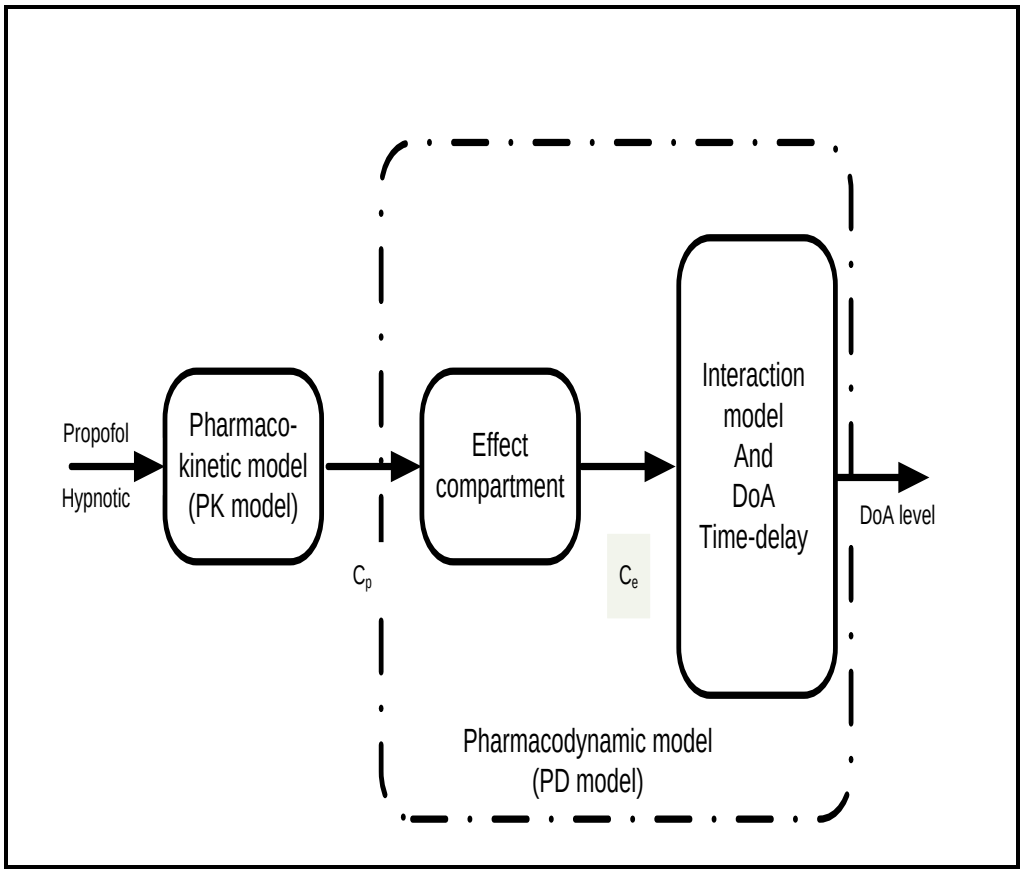

Figure 5.1: Depth of anaesthesia model for Smith predictive control

The total time-delay can be categorized into two parts. The first is related to the instrumentation parts, representing the time-delays at the instrument devices and the second are related to the dynamic response of the patient (non-instrumentation delay) as shown in Figure 5.2.

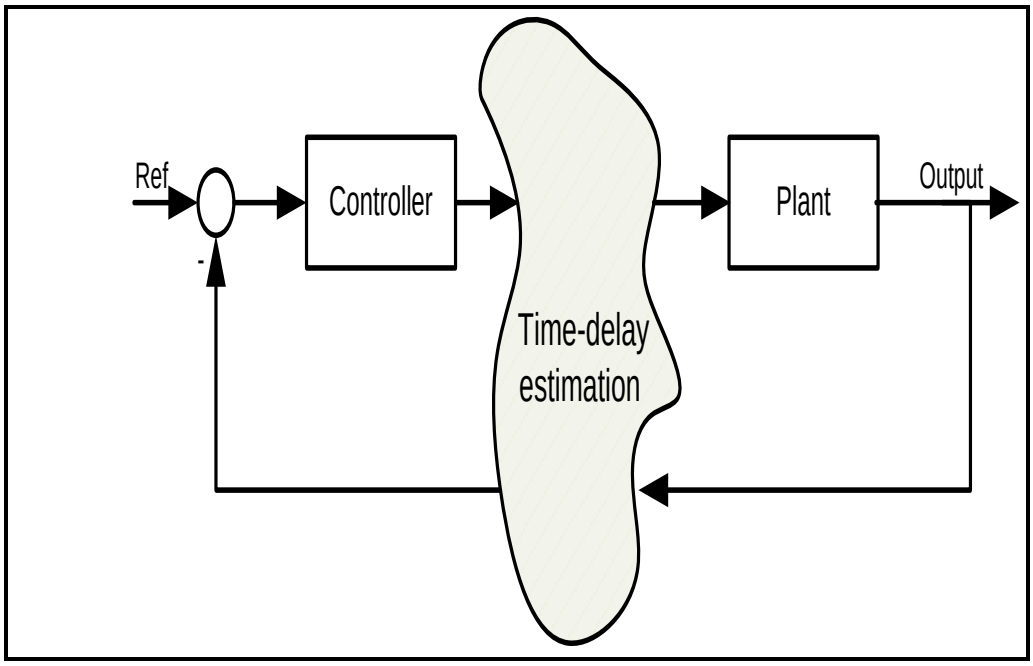

Figure 5.2: Feedback control system for SPC

5.1.1 Time-Delay estimation

During surgery, when the patient arrives at the intensive care unit, the desired BIS target should be 50 and must remain between 40 and 60 for a good sedation level. At around 50 BIS can be approximated linearly by a line, using this relationship:

$$\mathrm{BIS}(t) = a\, C_e(t) + b \tag{5.4}$$

where a represents the slope of the linear approximation and b is a constant.

The real values of the parameters for the selected 12 patient sets given in Table 5.1 have been taken from Yelneedi, Samavedham & Rangaiah (2009) and the simulated BIS signals were obtained based on the scheme presented in Figure 5.3. The Propofol infusion is applied to the patient and the real BIS signal is recorded by the BIS

Table 5.1: Values of the parameters for the 12 patients sets arranged in the decreasing order of their BIS sensitivity to Propofol infusion

Parameter									
Patient no.		k_{10}	k_{12}	k_{21}	k_{13}	k_{31}	k_{e0}	EC_{50}	γ
(sensitive)	1	0.08925	0.084	0.06875	0.031425	0.004125	0.459	1.6	2
	2	0.14875	0.14	0.04125	0.052375	0.004125	0.239	1.6	2
	3	0.14875	0.112	0.04125	0.0419	0.004125	0.239	1.6	3.133
	4	0.14875	0.14	0.04125	0.052375	0.004125	0.239	1.6	3.133
	5	0.08925	0.084	0.04125	0.052375	0.002475	0.459	2.65	2.551
	6	0.14875	0.112	0.06875	0.031425	0.002475	0.459	2.65	2.551
(nominal)	7	0.119	0.112	0.055	0.0419	0.0033	0.349	2.65	2.551
	8	0.119	0.112	0.055	0.0419	0.0033	0.239	2.65	2
	9	0.119	0.112	0.055	0.0419	0.0033	0.349	2.65	2.551
	10	0.08925	0.084	0.06875	0.031425	0.002475	0.459	3.7	2
	11	0.14875	0.112	0.06875	0.031425	0.002475	0.349	3.7	2.551
(insensitive)	12	0.08925	0.084	0.04125	0.052375	0.002475	0.239	3.7	3.133

monitor. The same Propofol infusion rate is used in the simulator to obtain the simulated BIS signal. Using the PK-PD patient model, the effective concentration of the drug is calculated. The simulated BIS signal is related to the effective concentration of the drug by the Hill curve. A delay is added to simulate the time-delay introduced by the real monitor.

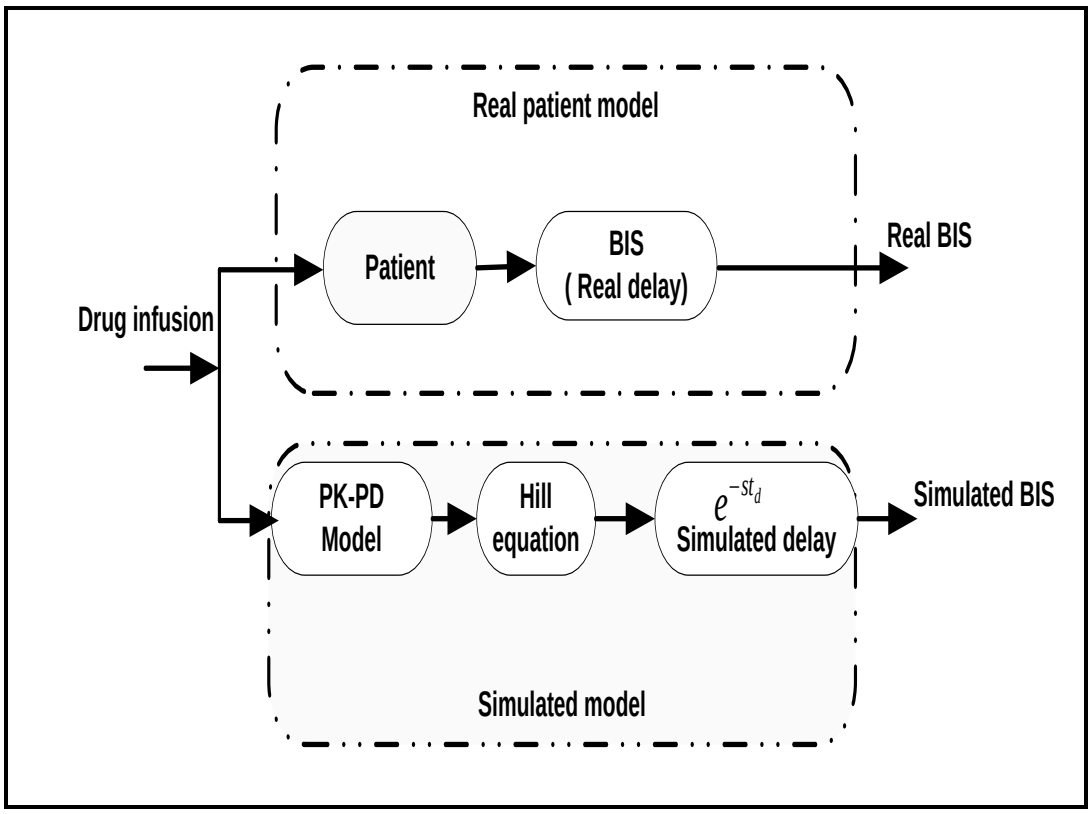

Figure 5.3: The representation of the real and simulated BIS

With the time-delay introduced by the BIS monitor, the real BIS signal can be expressed by the following relationship (Robayo et al. 2010):

$$\mathrm{BIS}(t) = a\, C_e(t-\tau) + b \tag{5.5}$$

If there are no disturbances, the simulated BIS signal can be expressed by:

$$\hat{\mathrm{BIS}}(t) = \hat{a}\, C_e(t-\hat{\tau}) + \hat{b} \tag{5.6}$$

where: a and $\hat{a}$ are the slopes of the linear curve for real and simulated cases, correspondingly, b and $\hat{b}$ represents the intersection of the line with the BIS axis

for the real and simulated cases, correspondingly, τ and $\hat{\tau}$ are the time-delays in samples for the real and the simulated cases, respectively.

If $(\tau - \hat{\tau})$ is the difference between the time-delay of the real BIS signal and the time-delay of the simulated BIS signal, the linear relation between real BIS and simulated BIS is obtained by (Robayo et al. 2010):

$$\mathrm{BIS}(t) = \tilde{a}\,\hat{\mathrm{BIS}}(t - \tilde{\tau}) + \tilde{b} \tag{5.7}$$

where $\tilde{a} = a/\hat{a}$, $\tilde{b} = b - (\hat{b}/\hat{a})a$, $\tilde{\tau} = \tau - \hat{\tau}$.

$\tilde{a} = 1$, $\tilde{b} = \tilde{\tau} = 0$ in the case that the two signals are not influenced by noise or disturbances (Robayo et al. 2010).

Advanced control techniques such as SPC can successfully deal with variable time-delay, nonlinearities, and input and output constraints (Kaya 2004). Since SPC relies on the availability of a patient model, it is important to provide accurate information to the controller in order to maximize its performance. In the case of anaesthesia, the TD varies between 40–180 seconds, and it is important that its value is known at all times and taken into account by the control strategy (Ionescu, Hodrea & De Keyser 2011).

The PD function, which captures the effect dynamic, is modified in order to account for the time-delay that exists between the administration of the drug and the onset of effect. The anaesthesia sensor dynamics is now a distinct part of the model,

which allows other sensing technologies to be used in conjunction with the PD models identified using the proposed approach (Sreenivas et al. 2009). However, unless the time-delay dynamics are expressed as rational linear time invariant (LTI) transfer functions (e.g., using Pade approximation), the uncertainty related to the time-delay cannot be directly expressed as parametric uncertainty (Dumont, Martinez & Ansermino 2009).

5.1.2 Identifying the PK time-delay

Inter-patient variability plays a important role in the overall system uncertainty (Bibian 2006). For example, there is a significant difference in the PK time delay and PD time constant between patients. The time-delay cannot be directly expressed, unless the time-delay is expressed as a function of patient's parameters such as the inverse of the effect-site compartment time constant (k_{e0}), the half-maximal effective concentration (EC_{50}) and the steepness of the curve γ. While the EC_{50} variability is more limited, its effect is still about 6-times difference in terms of the overall PK-PD steady state gain (Bibian 2006). In other words, the effects of the PD parameters have a significant influence compared with PK parameters. PD identification during induction, however, may not be practical due to a large number of factors that can affect the anaesthesia time course (Bibian 2006). Therefore, self-tuning of the model parameters during induction may thus be limited to specific situations that require trained human operators to assess the validity of the identification data and the derived PD parameters. An alternative to a full identification procedure is to only identify specific PK-PD parameters. Note that

the identification, when identifying the PK time delay, directly translates into significant improvements in terms of control performance (Muñoz et al. 2004).

5.2 Smith Predictor and Controller Design

The Smith Predictor Controller is able to compensate for the dead time through the use of the mathematical model of the process and its dead-time or time-delay to feedback to the primary controller, what the process variable would have behaved without the delay. In systems with large delays, performance can also be improved by using a Smith Predictor Controller structure that compensates for the nominal time-delay. This time-delay compensation allows an increase in the controller bandwidth, which results in improved performance. However, the performance of the Smith predictor largely depends on the accuracy of the process model.

The Smith Predictor makes use of the nominal model of the system in order to compensate for the delay. See Figure 5.4. The zero-delay nominal model is simulated based on the same infusion rate that is entered into the system. As such, the model output represents the predicted delay-free response of the system. This response is then compared to the response with delay. The result of this comparison is a signal that represents the future system response to the control action. This signal is then added to the feedback signal. As a result, the controller can be designed based on a delay-free model, which results in added stability in the control loop that can be further used to increase the controller bandwidth. While the inherent limitation of a delayed system is still present, the increased control bandwidth usually results in increased stability and better performances.

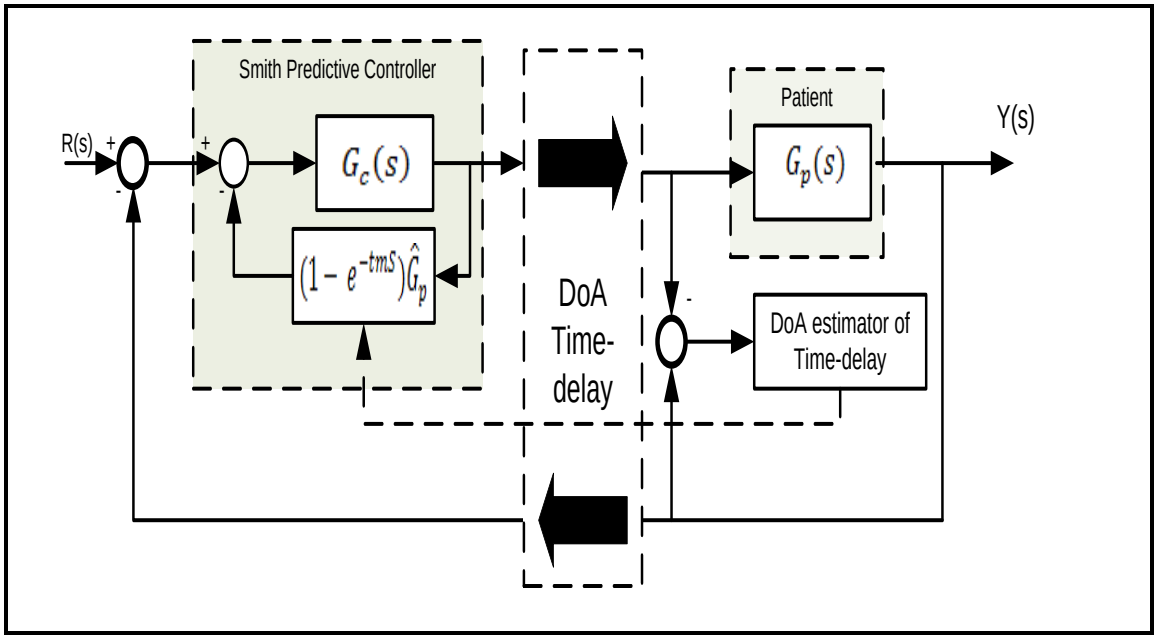

Figure 5.4: The block diagram of Smith predictive control

However, in systems presenting the large gain uncertainty, this technique potentially results in larger over-and under-shoots. For instance, if the gain of the nominal model is an order of magnitude different from that of the real system, the SPC structure may result in either under- or over-compensation, which is not desired. The SPC proposed a control structure to compensate for the time-delay shown in Figure 5.5. By using this structure, the effect of the time-delay in the system can be properly removed. As shown in Figure 5.5, $G_c(s)$ is the controller, the $G_p(s)$ denotes the transfer function of the patient without time-delay and $\widehat{G}_p(s)$ is the estimation model of DoA, t_p is the time-delay of the patient response, and t_m is the time-delay of measurement. The transfer function is obtained in the following equation:

$$\frac{Y(s)}{R(s)} = \frac{G_c(s)G_p(s)e^{-t_pS}}{(1 + \hat{G}_p(s)G_c(s) + G_c(s)G_p(s)e^{-t_pS} - \hat{G}_p(s)G_c(s)e^{-t_mS})} \quad (5.8)$$

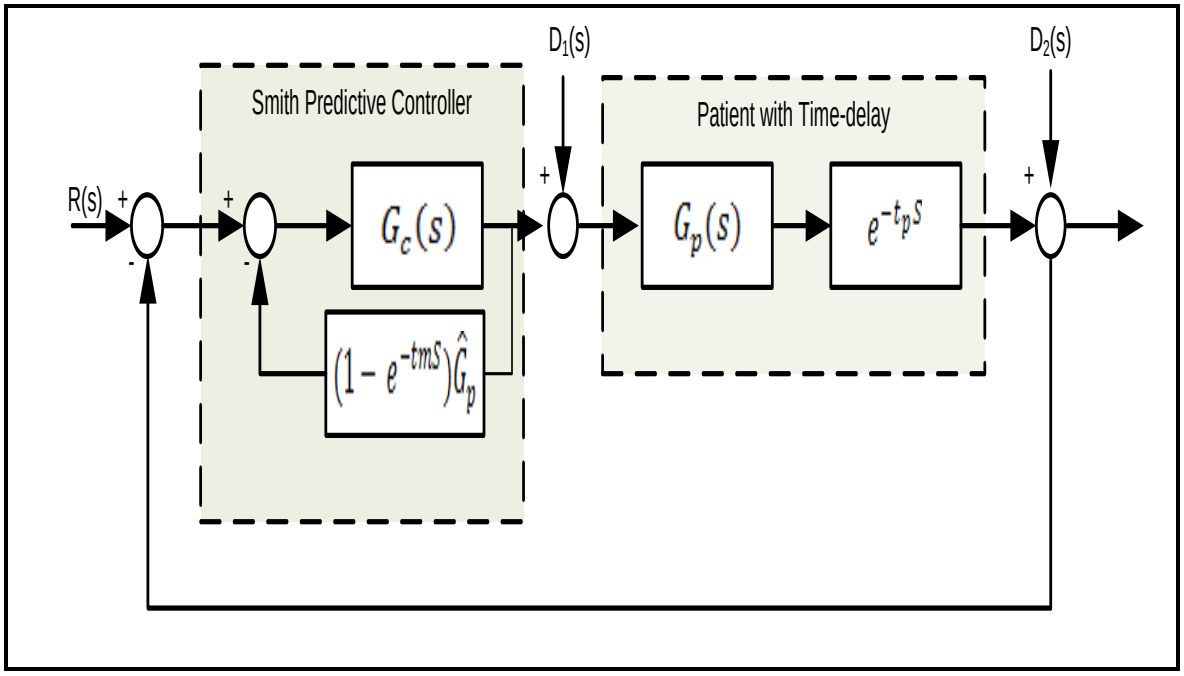

Figure 5.5: The control system structure with the Smith predictor

In Figure 5.5, the part with the dotted line is the SPC and its transfer function obtained as below:

$$G(s) = \frac{G_c(s)}{1 + (1 - e^{-tmS})\hat{G}_p(s)G_c(s)} \quad (5.9)$$

When $\widehat{G}_p(s) = G_p(s)$ and $t_m = t_p$ and then equation (5.9) becomes:

$$G(s) = \frac{Y(s)}{R(s)} = \frac{G_c(s)G_p(s)e^{-t_pS}}{1 + G_c(s)G_p(s)} \quad (5.10)$$

where $G_p(s)$ is the patient model and consist of two parts, PK and PD (Yelneedi, Samavedham & Rangaiah 2009).

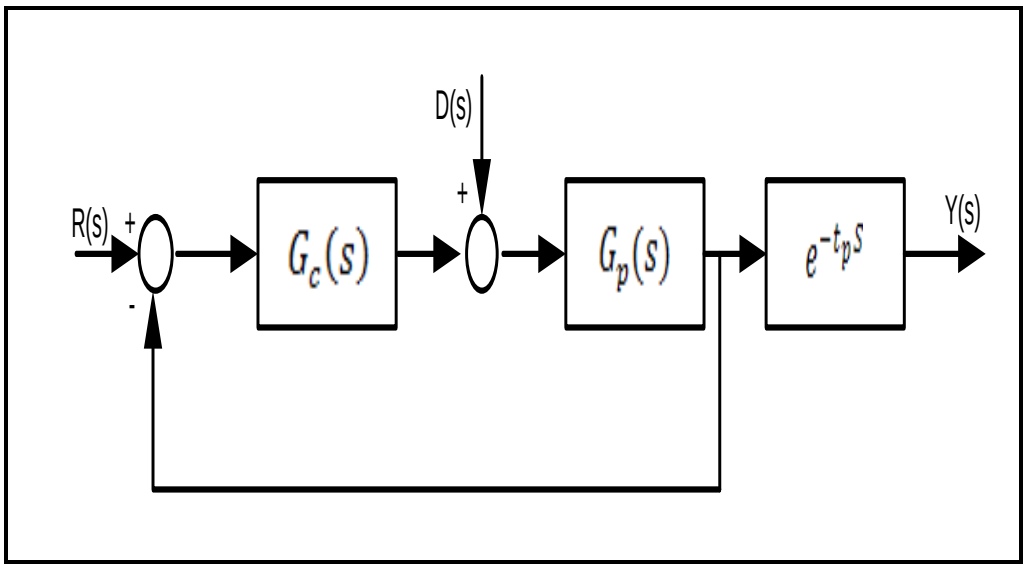

Figure 5.6 The equivalent block diagram by applying the Smith predictor

We can see from equation (9.10) that the complicated transformation of the time-delay will turn into two simple parts. One part is the transfer function of the system without the impact of the time-delay. The second part is just the simple time-delay. The equivalent block diagram of equation (9.10) is shown in Figure 5.6. Note that in the Figure 5.6, no exponential term exists and the value of the system is not affected by the time-delay. Thus, the system will present the same closed-loop performance without the time-delay, only with the pure input time-delay t_p. The Smith Predictor Controller is used when DoA (the patient and instrumentation) time-delays are significant as $t_p = t_m$.

5.3 Performance Evaluation in Simulation

The study was performed on a data set of 12 patients of 20–50 years old. The data was obtained from reference (Yelneedi, Samavedham & Rangaiah (2009). The values for nominal patient obtained for the pharmacokinetics model were k10 = 0.119, k12 = 0.112, k21 = 0.055, k13= 0.0419, k31= 0.0033, ke0 = 0.349, EC50= 2.56, $\gamma = 2.5$, as shown in Table 5.1. The adjustment of the controller gains was made in a simulation way trying to get a smooth transitory and a stable response. For validation purposes, a representation of the real BIS signal "signal without time-delay" was built. A time-delay was added to the simulator in order to represent the delay introduced by the BIS monitor. Thus, after several trials adequate values for SP Controller set values were tested in the whole population of the study. Figures 5.7, 5.8, 5.9 and 5.10 present the evolution of the anaesthesia for three different patients as shown in the simulation model in Figure 5.11. The controller parameters are adjusted depenging on the error between the system output (BIS) and the model reference output defined for this closed-loop.

The SPC has to maintain BIS between 40 and 60 during the surgery. As well, it is very important to maintain the drug concentration within the acceptable limits in the patient's body. The delay signal is then added to the feedback signal. As a result, the controller based on a delay-free model, which results in added stability in the control loop that can be further used to increase the controller bandwidth. As far as the implementation of the SP is concerned, the nominal time-delay is now replaced by the identified time-delay.

When a patient experiences significant time-delay, it is quite common to augment the controller with a Smith Predictor, a construction that removes the delay term from the characteristics polynomial of the closed loop.

The current work shows that patient and instrumentation time-delays play an important role in controlling the depth of anaesthesia performance. In Figure 5.7, it is possible to observe the effect of the time-delay by applying the proposed algorithm. This improves the overall performance of the SPC controller compared with the performance of PID controller regarding overshoot, undershoot and settling time.

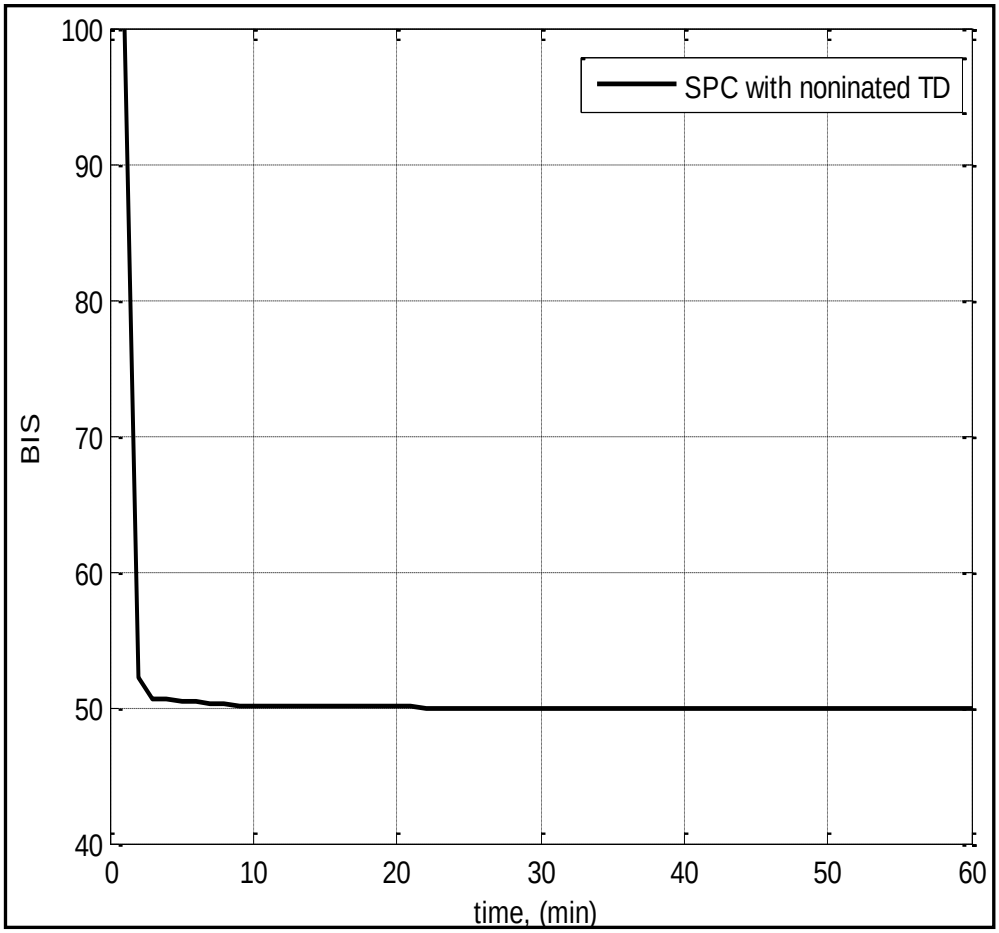

Figure 5.7: Smith predictor with nominated time-delay

In Figures 5.8, 5.9 and 5.10 an insensitive patient requires relatively more drug dosage and responds more slowly to the drug. For the sensitive patient, the nominal patient model predicts a lesser concentration than the actual concentration because it infuses fewer drugs based on the larger gain BIS response to Propofol infusions. It should be mentioned here that the novelty of the current work is that the time-delay model can be used for different types of drugs.

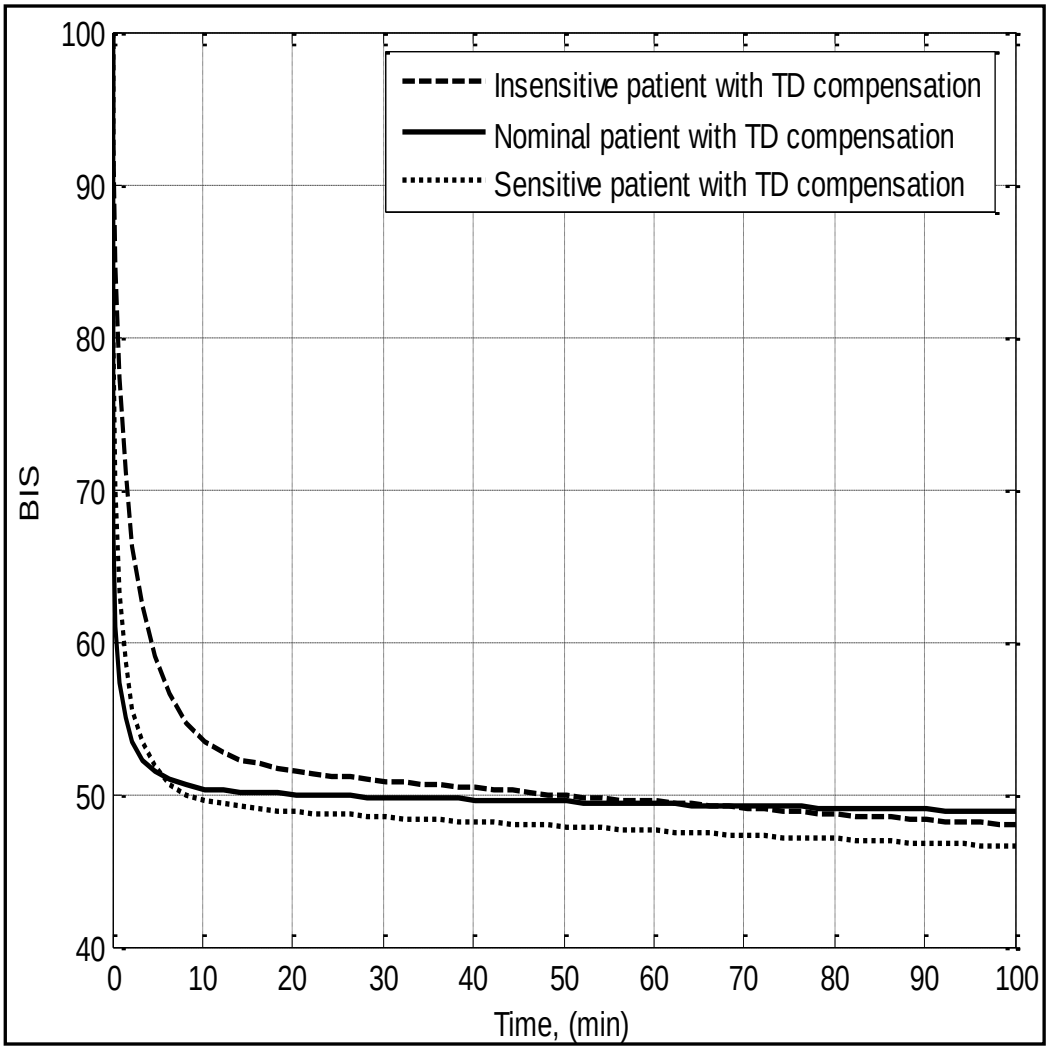

Figure 5.8: Smith predictor without time-delay

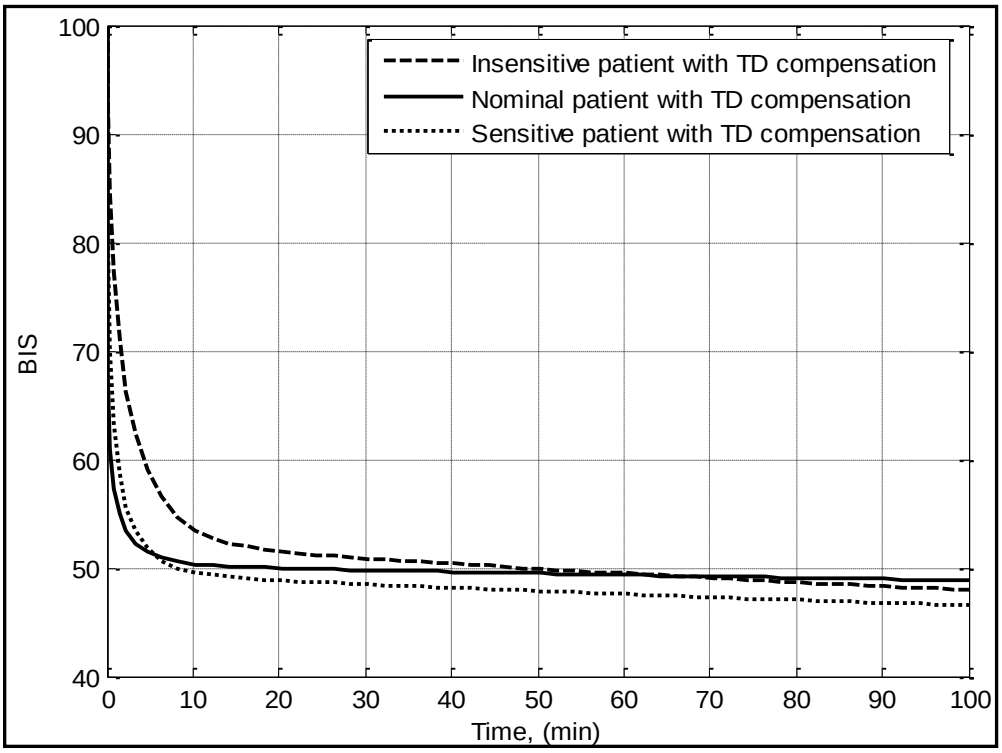

Figure 5.9: Smith predictor with time-delay for three different patients

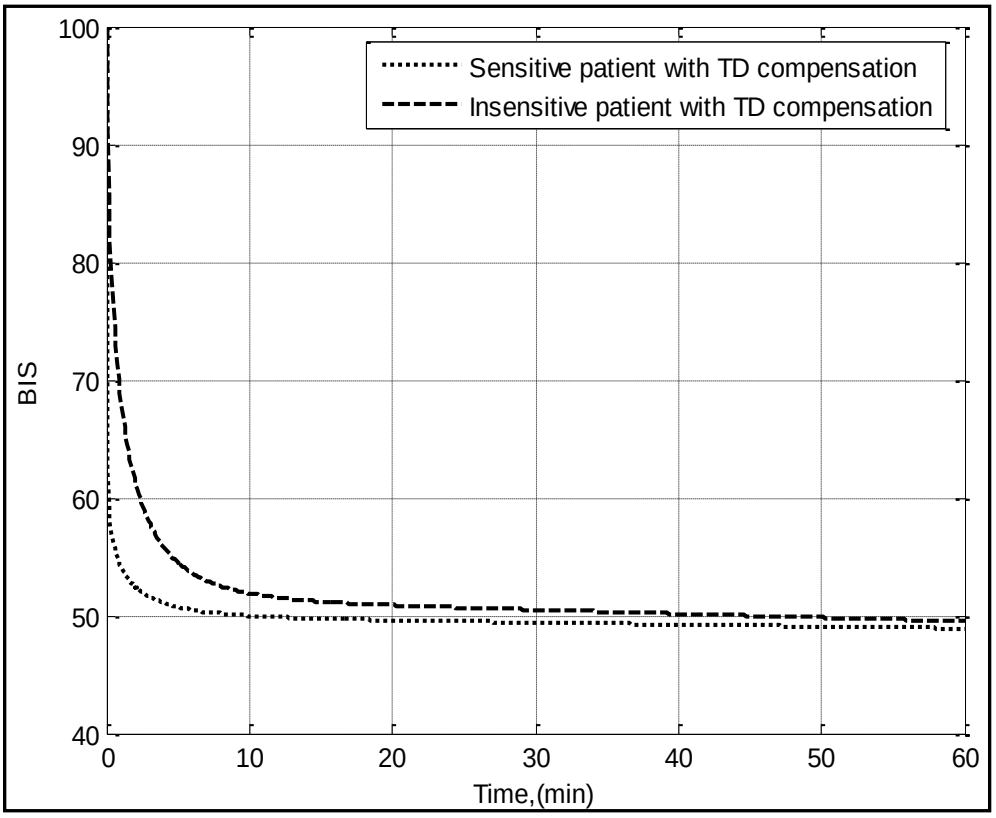

Figure 5.10: Smith Predictor with time-delay for two different patients

The configuration of this controller can be seen in Figure 5.11.

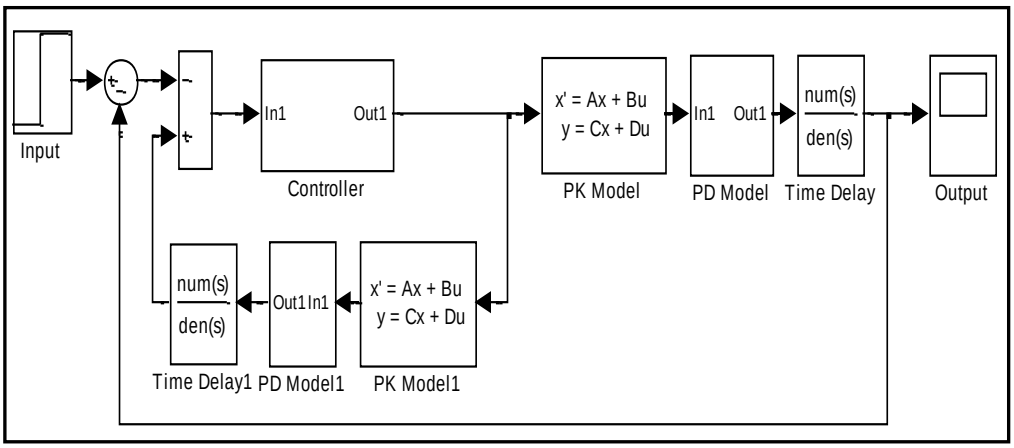

Figure 5.11: Smith predictive control simulation's block diagram

Figures 5.12 and 5.13 present the performance of the SPC for the infusion rate of Propofol and the predicted plasma Propofol concentration. In this case, the adjustable parameters are the static gain and the time constant of the approximated first-order model used in the Smith Predictor.

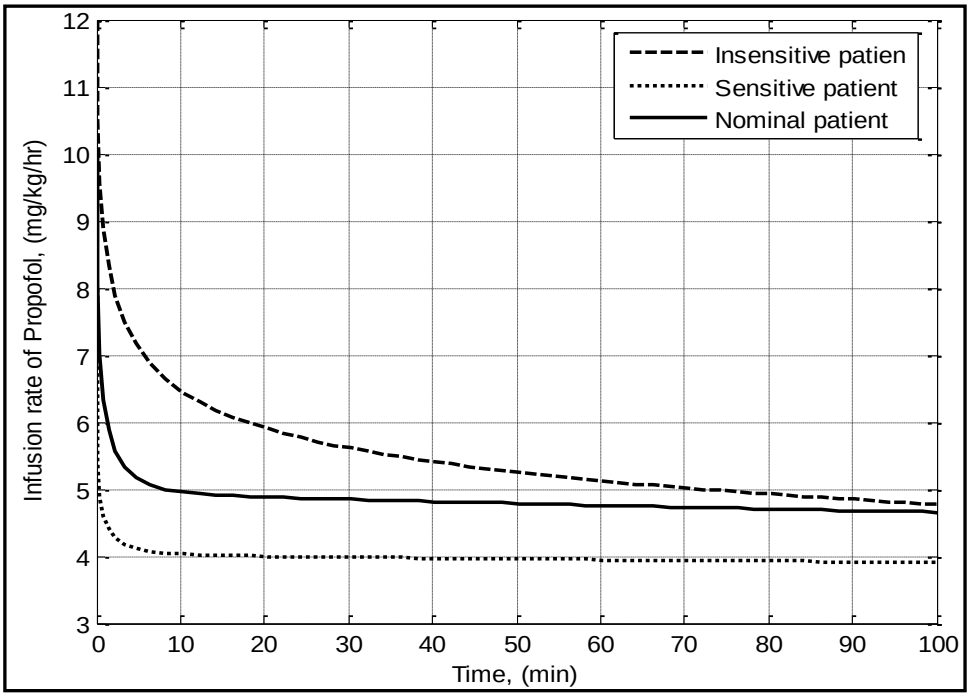

Figure 5.12: Performance of SPC for three different patients

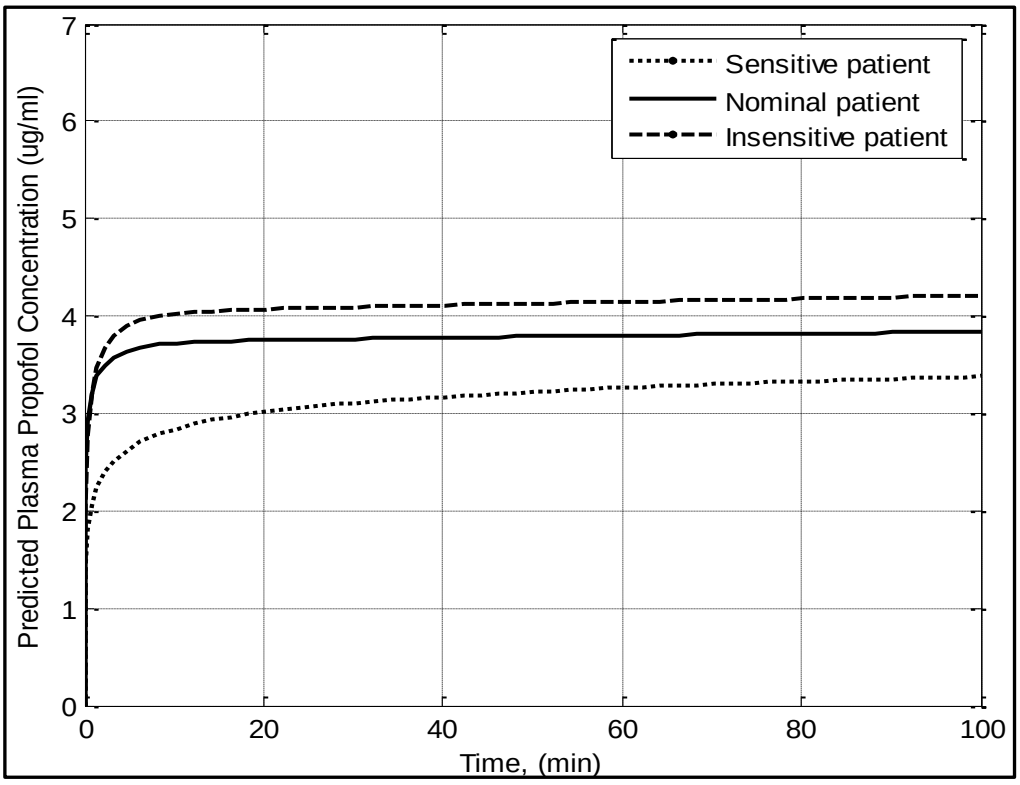

Figure 5.13: SPC for three different patients

5.4 Conclusions

In this chapter, the SPC has been introduced to estimate the TD originated from the patient and instrumentation (BIS monitor). The TD estimation algorithm is tested on a data set of 12 patients. The obtained results show that the time-delays play an important role in the depth of anaesthesia control performance. This study agrees with similar studies reported in literature (Yelneedi, Samavedham & Rangaiah 2009).

The estimation algorithms are based on the Smith Predictive Control and have been improved with time-delay compensation modules that notably improve the performance of the overall patient response. These models have been implemented in

simulation using Simulink and Matlab Control Toolbox. The results have been compared to the control without compensator. In the system performance, the settling time has been shorted to 30% and the overshoot and undershoot have been reduced by about 15%. To make the strategy applicable to different patients an adaptive scheme has been designed so that the controller adapts the algorithm to the dynamics of the specific patient. Also to further improve the system response the accuracy of the system model for DoA needs to be improved further.

CHAPTER 6

ROBUST DEADBEAT CONTROL FOR PATIENT MODEL WITH UNCERTAINTIES

6.1 Uncertainties and Disturbances in DoA Control

More recently, considerable efforts have been made to identify and control systems with uncertainty and nonlinearity in medical related control system. Westenskow (1997) developed a closed-loop PID controller to control the depth of anaesthesia. Sakai et al. (2000) employed a closed-loop PID control system for Propofol administration using BIS (Bispectral Index) as the controlled variable. Both of them concluded that their systems provided intra-operative hemodynamic stability and a prompt recovery from the sedative-hypnotic effects of Propofol. Absalom et al. (2002) developed a similar closed-loop PID controller using BIS as the controlled variable, and a Propofol targeting central plasma concentration-controlled infusion system as the control actuator. The authors concluded that further studies were

required to determine if control performance could be improved by changing the proportional gains of the PID controller or by using an effect-site-targeted Propofol controlled infusion system. Later, they modified their control algorithm to a target-controlled infusion (TCI) system that regulated effect-site concentration, and proved it more efficient. However, PID controllers still faced some stability problems (Absalom & Kenny 2003).

This study applies the deadbeat robust control technique to the depth of anaesthesia. First, a DoA model is build up based on the literature review. This model is a single-input-single-output (SISO) system with nonlinear component. Then, a PID-based robust deadbeat control scheme is applied to the SISO systems, and a deadbeat controller is designed. The robust deadbeat controller can tolerate system parameter uncertainty for up to $\pm 50\%$ (Dawes et al. 1994). The additions of the extra gains permit the designer more flexibility for making any plant work with this method. This feature is used to deal with the uncertainty of the DoA model. The proposed method is implemented and evaluated in simulation. Compared with the other two different PID based control systems, the proposed method has less over and undershoot, shorter settling time and is more robust to parameter change caused disturbances.

6.2 Patient Model with Uncertainties

First we consider the drug modeling approach and how the administered drug distributes around the body. This step leads to a pharmacokinetic model (PK) which can be used to predict the blood plasma concentration of the drug (Alonso, Lemos & Mendonca 2008). The second step is the mathematical expression related

to concentration of the drug effect itself. This expression is referred to as pharmacodynamic model (PD) (Bibian 2006).

Pharmacokinetics is the study of the absorption, distribution, metabolism and elimination of drugs by the body (as shown in Figure 6.1). The pharmacokinetic model of a drug is a mathematical term relating to the drug blood plasma concentration $C_p(s)$ to the administered dose $u(s)$. The aim of this section is thus to define the transfer function of $PK(s)$:

$$PK(s) = \frac{C_p(s)}{u(s)} \tag{6.1}$$

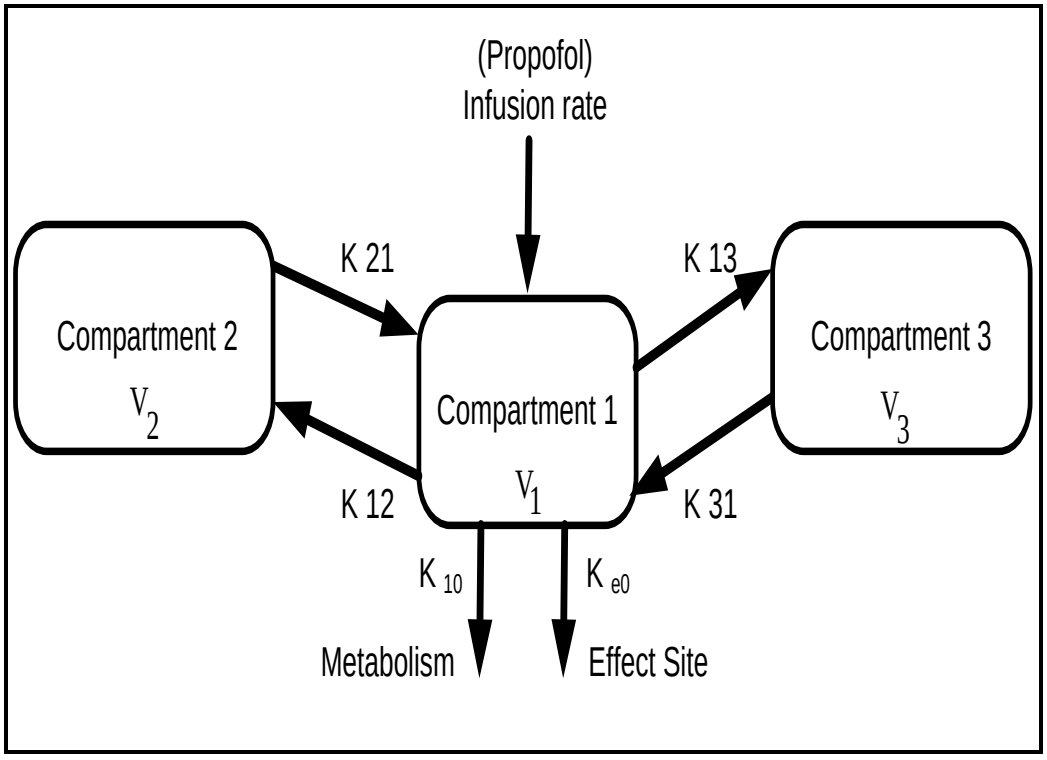

Figure 6.1: The pharmacokinetic model

The PK can be expressed as a time course of the concentration of any given drug within the plasma and other tissues of the human body. Throughout the absorption phase following an intravenous bolus administration, the anaesthetic (Propofol) mixes quickly within the central blood pool, resulting in a plasma peak concentration (Bailey & Haddad 2005). A delay elapses between the actual injection of the anaesthetic (Propofol) and its mixing within the blood pool. Systemic circulation then distributes the anaesthetic to a variety of tissues within the body (Alonso, Lemos & Mendonca 2008).

The time course of the concentration for most drugs, within the blood plasma after the intravenous administration and uptake can be fitted to resemble a decaying function, with two distinct modes corresponding to the distribution and elimination phase respectively. This behaviour can be expressed mathematically as:

$$C_p(t) = Xe^{-At} + Ye^{-Bt} \qquad (\mu g/ml) \tag{6.2}$$

where $C_p(t)$ is the drug plasma concentration expressed in microgram per millilitre (Propofol), A is the rate constant of the distribution phase, B is the rate constant of the elimination phase.

In many cases, a tri-exponential model will capture the kinetics of the drug much better (Alonso, Lemos & Mendonca 2008).

$$C_p(t) = Xe^{-At} + Ye^{-Bt} + Ze^{-Ct} \qquad (\mu g/ml) \tag{6.3}$$

where Z and C describe the fast dynamics corresponding to the distribution phase.

A main advantage of exponential models is that they can be simply derived using graphical means. The identification can be carried out directly by using either bolus data or analysing the decaying blood plasma characteristic, or by using infusion data and analysing how the plasma concentration increases over time (Alonso, Lemos & Mendonca 2008).

In terms of control and system engineering, the exponential model in equation (6.3) can be directly expressed as:

$$PK(s) = \frac{\mathrm{C_p(s)}}{\mathrm{u(s)}} = \frac{X}{(s+A)} + \frac{Y}{(s+B)} + \frac{Z}{(s+C)} \tag{6.4}$$

The total amount of the anaesthetic delivered into compartment one ($\mathrm{C_1}$) is eliminated according to the rate constant $\mathrm{k_{10}}$. The anaesthetic is distributed in the other two compartments ($\mathrm{C_2}$, $\mathrm{C_3}$) at a rate of $\mathrm{k_{12}}$ and $\mathrm{k_{13}}$. The concentration of $\mathrm{C_1}$ decreases quickly whiles the concentrations of $\mathrm{C_2}$ and $\mathrm{C_3}$ increase. Once the concentrations in compartment one and any of the peripheral compartments ($\mathrm{C_2}$, $\mathrm{C_3}$) attain and reach equilibrium, the distributive process setback and the anaesthetic stored in the peripheral compartment returns to the central compartment at the rate of $\mathrm{k_{21}}$ or $\mathrm{k_{31}}$. Because the blood of compartment one acts as a transporter for the anaesthetic, there is no direct exchange between the two peripheral compartments. In other words, only the anaesthetic presents in compartment one can be eliminated (Bibian 2006).

The mathematical expressions in a state space representation can be obtained by writing the mass balance equations in (6.5) and (6.6):

$$\begin{bmatrix} \dot{C_1}(t) \\ \dot{C_2}(t) \\ \dot{C_3}(t) \end{bmatrix} = \begin{bmatrix} -k_{10} - k_{12} - k_{13} & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{bmatrix} \begin{bmatrix} C_1(t) \\ C_2(t) \\ C_3(t) \end{bmatrix} + \begin{bmatrix} \frac{1}{V_1} \\ 0 \\ 0 \end{bmatrix} u\,(t) \tag{6.5}$$

$$C_p(t) = [1 \quad 0 \quad 0] \begin{bmatrix} C_1(t) \\ C_2(t) \\ C_3(t) \end{bmatrix} \tag{6.6}$$

where V_1 is the volume of compartment one. Also, by definition, the plasma blood concentration equals the drug concentration of compartment one, i.e., $C_p(t) = C_1(t)$.

In order to simplify the $PK(s)$ model as a SISO transfer function using both the exponential and compartmental parameters as in equation (6.6) (GentiliniRossoni-Gerosa, et al. 2001):

$$PK(s) = \frac{C_p(s)}{u(s)} = \frac{(s + k_{21})(s + k_{31})}{V_1(s + A)(s + B)(s + C)} \tag{6.7}$$

The function of the PD model is to mathematically express the observed effect of a drug as a low-pass filter is used to relate the Propofol plasma concentration as shown in Figure 6.2 (Alonso, Lemos & Mendonca 2008):

$$PD(s) = \frac{E(s)}{C_p(s} \tag{6.8}$$

where $\mathrm{PD(s)}$ is the pharmacodynamic model and $\mathrm{E(s)}$ is the drug effect.

The effect-site concentration is related to DoA as Hill equation (Dumont, Martinez & Ansermino 2009).

$$E(t) = E_0 - E_{max}\left[\frac{{C_e}^{\gamma}(t)}{({C_e}^{\gamma}(t) + EC_{50}^{\gamma})}\right] \tag{6.9}$$

The mathematical expression of the effect site drug concentration $\mathrm{C_e(s)}$ is a function of the plasma concentration $\mathrm{C_p(s)}$ as in equation (6.10):

$$C_e(s) = \left[\frac{k_{e0}}{(s + k_{e0})}\right] C_p(s) \tag{6.10}$$

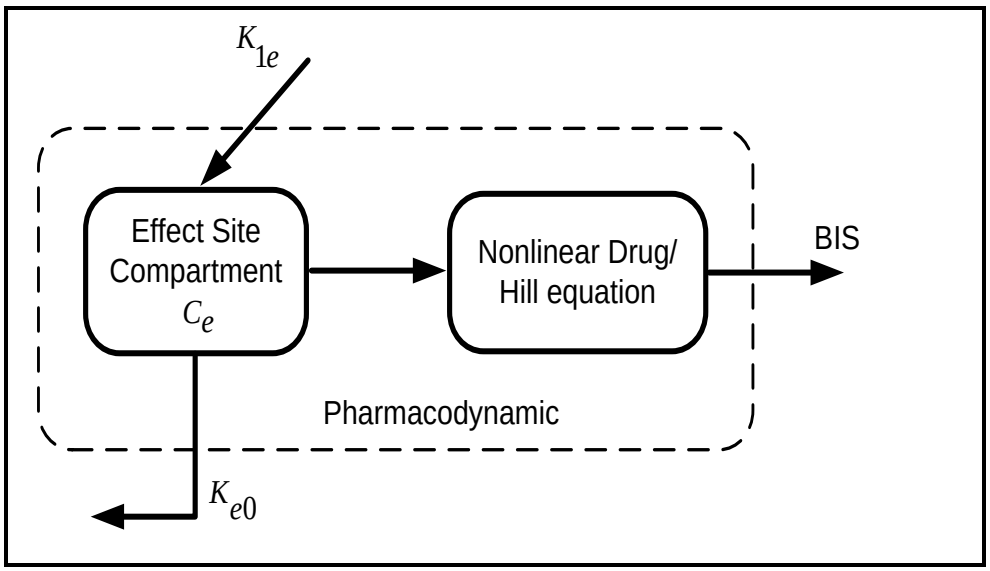

Figure 6.2: The pharmacodynamic model

6.3 Robust Deadbeat Control (RDC) Technique

Figure 6.3 shows the basic structure of the robust deadbeat control system, and Table 6.1 is the deadbeat controller coefficients and response times. This technique initially works only for lower-order plants (Wen & Lu 2008). If a higher–order plant system is considered, then there is a need for higher gain. In this design, the controller could cope up to 50% variations and uncertainties in plant parameters (Dawes et al. 1994). With changes in patients' PK and PD parameters (k_{10}, k_{12}, k_{13},. EC_{50}, γ and k_{e0}) from 10% to 20%, 30%, 40% up to 50%, the robust deadbeat controller is still able to tolerate the changing parameters.

The deadbeat controller design and derivation method utilizes the following procedures. First, using a PID controller as $G_c(s)$, and then adding a cascade gain K before the PID controller. Second, add a state variable feedback gain K_a, that will make the system over-specified by at least one variable. Third, determine the number of poles for $G_cG(s)$, where n_p equals the number of poles in $G_cG(s)$. Refer to the Figure 6.3 feedback H(s) depending on the number of poles in $G_cG(s)$. The following steps are involved with this method:

1. H(s) = 1 for $n_p = 2$
2. $H(s) = 1 + K_b s$ for $n_p = 3$ or 4
3. $H(s) = 1 + K_b s + K_c s^2$ for $n_p = 5$

Then select gains, using the coefficients from Table 6.1, to achieve the deadbeat response with the following requirements:

4. Set K = 1
5. Set $\omega_n = T_s'$/(80% of the desired settling time)
6. The characteristic equation of the closed loop transfer equation will be equal to:

$$s^{n_p} + \alpha\omega_n s^{n_p-1} + \beta\omega_n^2 s^{n_p-2} + \gamma\omega_n^3 s^{n_p-3} + \cdots \ldots \ldots + \omega_n^{n_p}$$

7. The root of H(s) must be real and negative
8. The smallest root of H(s) will set the desired settling time by the relationship: [4/ (smallest root)] and be approximately equal to the desired settling time.

Then increase K until the response becomes deadbeat and the settling time is approximately equal to the desired value.

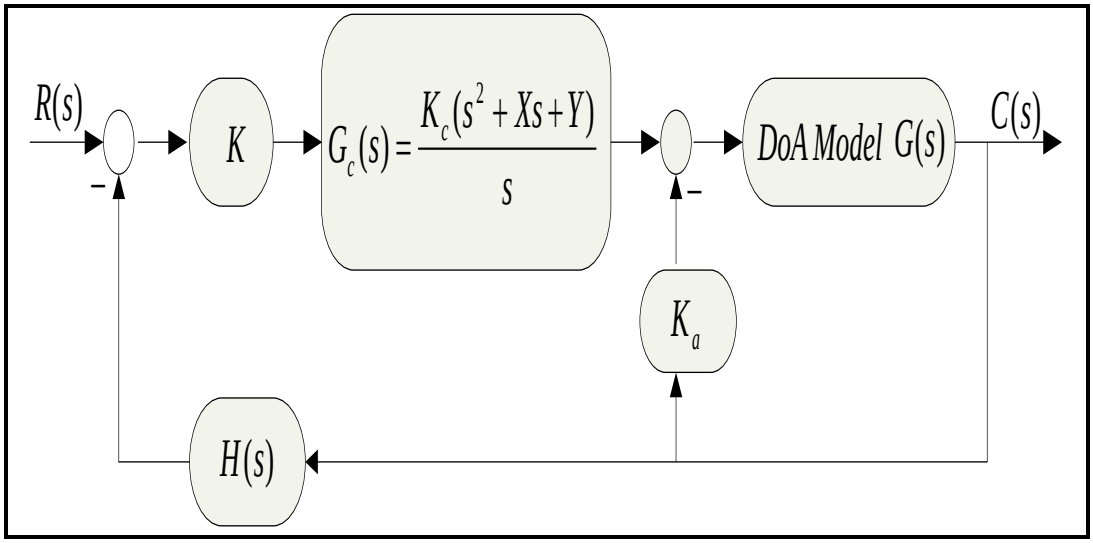

Figure 6.3: Robust deadbeat control structures

Table 6.1: Deadbeat coefficients and response times

Order (n_p)	α	β	γ	δ	$Tr_{90}{}'$	T_s'
2nd	1.82				3.47	4.82
3rd	1.90	2.20			3.48	4.04
4th	2.20	3.50	2.80		4.16	4.81
5th	2.70	4.90	5.40	3.40	4.48	5.43

The design procedure of a PID-based robust deadbeat control is shown below, taking fourth-order $F_1(s)$ and fifth-order $F_2(s)$ systems as examples

$$F_1(s) = \frac{\omega_n^4}{(s^4 + \alpha\omega_n s^3 + \beta\omega_n^2 s^2 + \gamma\omega_n^3 s + \omega_n^4)} \tag{6.11}$$

and

$$F_2(s) = \frac{\omega_n^5}{(s^5 + \alpha\omega_n s^4 + \beta\omega_n^2 s^3 + \gamma\omega_n^3 s^2 + \delta\omega_n^4 s + \omega_n^5)} \tag{6.12}$$

For equations (6.11) and (6.12), the coefficients α, β, γ and δ are selected from Table 6.1. Taking the fourth-order system first as an example and then using the same procedure with fifth-order system with a desired settling time 0.95 s, from Table 6.1 the normalized settling time can be found as:

$$T_s = \frac{4.81}{\omega_n}$$

Therefore ω_n can be found as:

$$T_s = \frac{4.81}{0.95} = 5.0632$$

The characteristic equation of the closed-loop transfer function of the forth-order systems is:

$$s^4 + \alpha\omega_n s^3 + \beta\omega_n^2 s^2 + \gamma\omega_n^3 s + \omega_n^4$$

From Table 6.1, α, β and γ can be found as:

$$\alpha = 2.20;\ \beta = 3.50;\ \gamma = 2.80$$

The transfer function of the forth-order systems is:

$$F_1(s) = \frac{657.183399}{s^4 + 11.139s^3 + 89.72448s^2 + 363.4314s + 657.183399}$$

To apply the deadbeat technique to the DoA model, first comparing the characteristic equation in equation (6.11), with the characteristic equations of different patients.

6.4 Applications of RDC to DoA Control

The block diagram of the DoA designed system is depicted in Figure6.4.

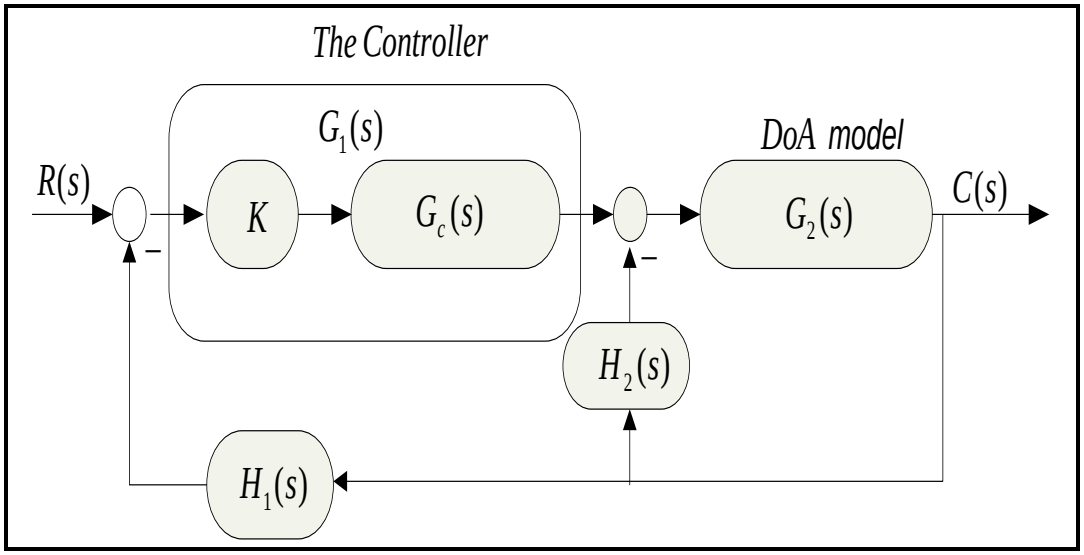

Figure 6.4: Robust deadbeat control structure for DoA

$$G_1(s) = KG_c(s) = \frac{K[K_c(s^2 + Xs + Y)]}{s}$$

$$G_2(s) = \frac{0.040382(s + 0.025992)(s + 0.0018266)}{(s + 0.37891)(s + 0.005896)(s + 0.0012622)}$$

$$H_1(s) = (1 + K_b s)$$

$$H_2(s) = K_a$$

The closed-loop control function for the DoA model can now be written as:

$$\frac{C(s)}{R(s)} = \frac{\mathrm{G_1(s)G_2(s)}}{1 + \mathrm{G_2(s)H_2(s) + G_1(s)G_2(s)H_1(s)}}$$

Then, use the technique initially proposed by Dorf et al. (Dawes et al. 1994), to determine these parameters. The characteristic equation of the above transfer faction is equal to the characteristic equation of the deadbeat transfer function. By using the characteristic equation of the deadbeat transfer function to obtain the characteristic equation of the closed-loop transfer function of DoA as:

$$\mathrm{s^4 + \alpha\omega_n s^3 + \beta\omega_n^2 s^2 + \gamma\omega_n^3 s + \omega_n^4}$$

From Table 6.1,

$$\alpha = 2.20;\ \beta = 3.50;\ \gamma = 2.80$$

$$\omega_\mathrm{n} = \frac{\mathrm{T_s'}}{80\%\ \text{of the desired settling time}\ \mathrm{T_s}}$$

The desired settling time for DoA is 6 minutes, then ω_n can be found as:

$$\omega_\mathrm{n} = \frac{\mathrm{T_s'}}{\mathrm{T_s} \times 80\%} = \frac{4.81}{6 \times 60 \times 80\%} = 0.0167$$

Therefore the characteristic equation now can be written as:

$$s^4 + 0.03674s^3 + 9.76115 \times 10^{-4}s^2 + 1.304 \times 10^{-5}s + 7.7779 \times 10^{-8}$$

Let K equal 1, and then by compare the characteristic equation to find the variables as:

$$K_c = 1 \times 10^{-4}\ ;\ K_b = 1 \times 10^{-7}$$

$$X = 363 \times 10^4\ ;\ \ Y = 342.78 \times 10^4;\ \ K_a = -8.212$$

Increase K until the response becomes deadbeat and settling time becomes approximately to the desired value.

6.5 Simulation and Results

The proposed control schemes were implemented and evaluated, using Simulink and Matlab Control Toolbox, to thoroughly investigate the system performance.

Figure 6.5 shows the implementation of the deadbeat DoA control system.

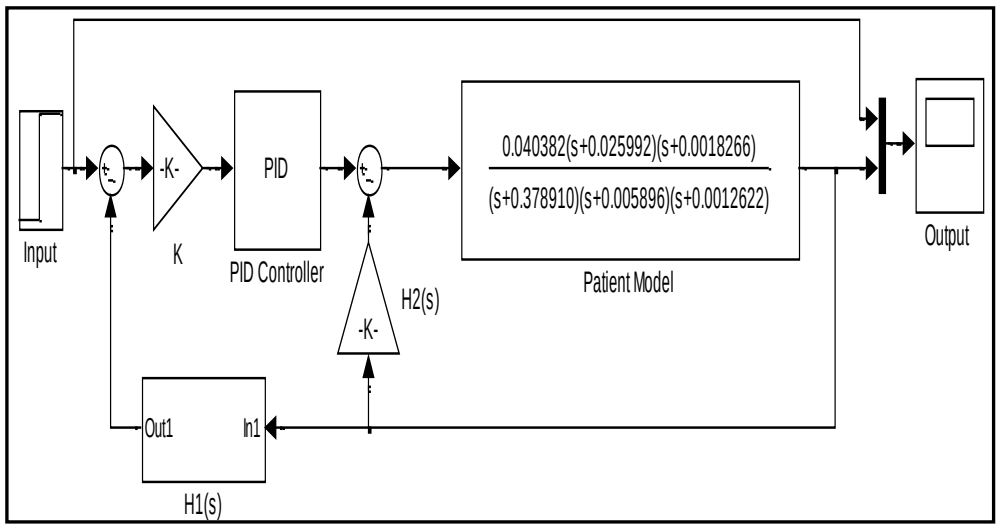

Figure 6.5: Implementation of a robust deadbeat control structure for DoA

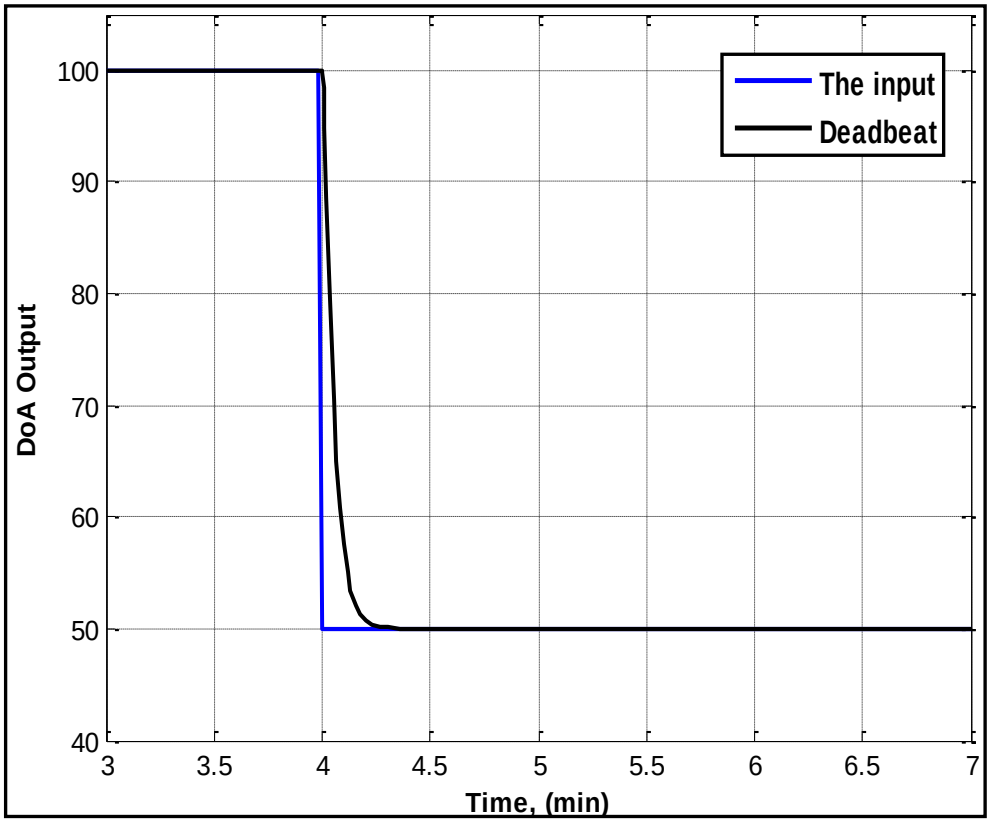

Figure 6.6: DoA robust deadbeat control response

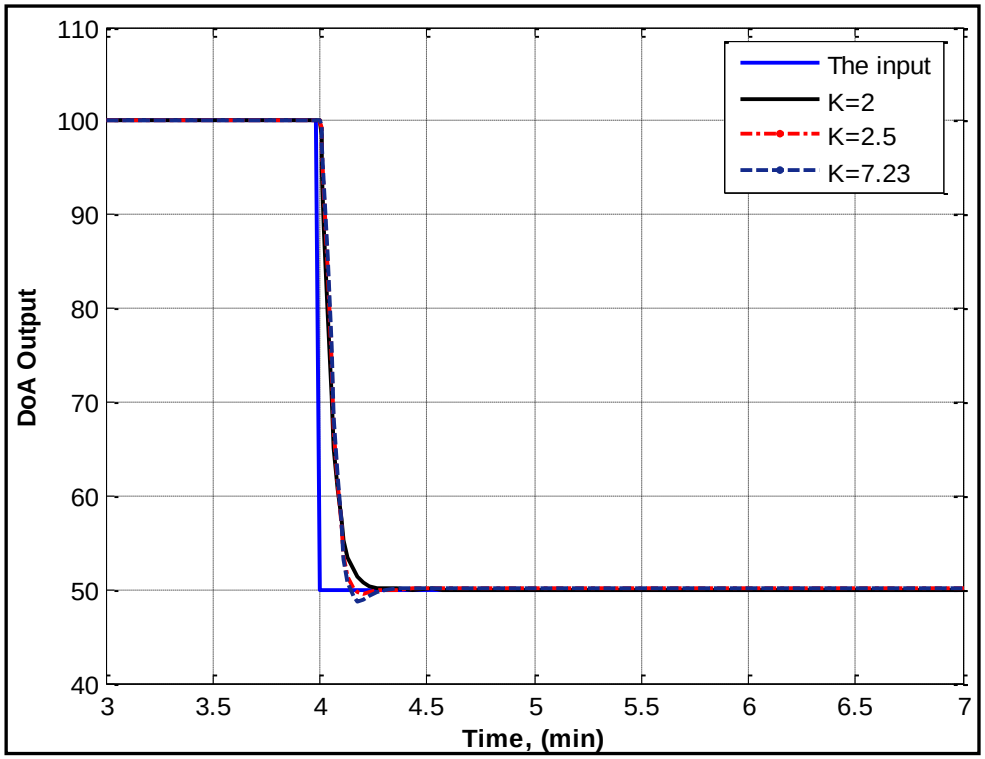

Figure 6.7: DoA robust deadbeat control response for different values of K

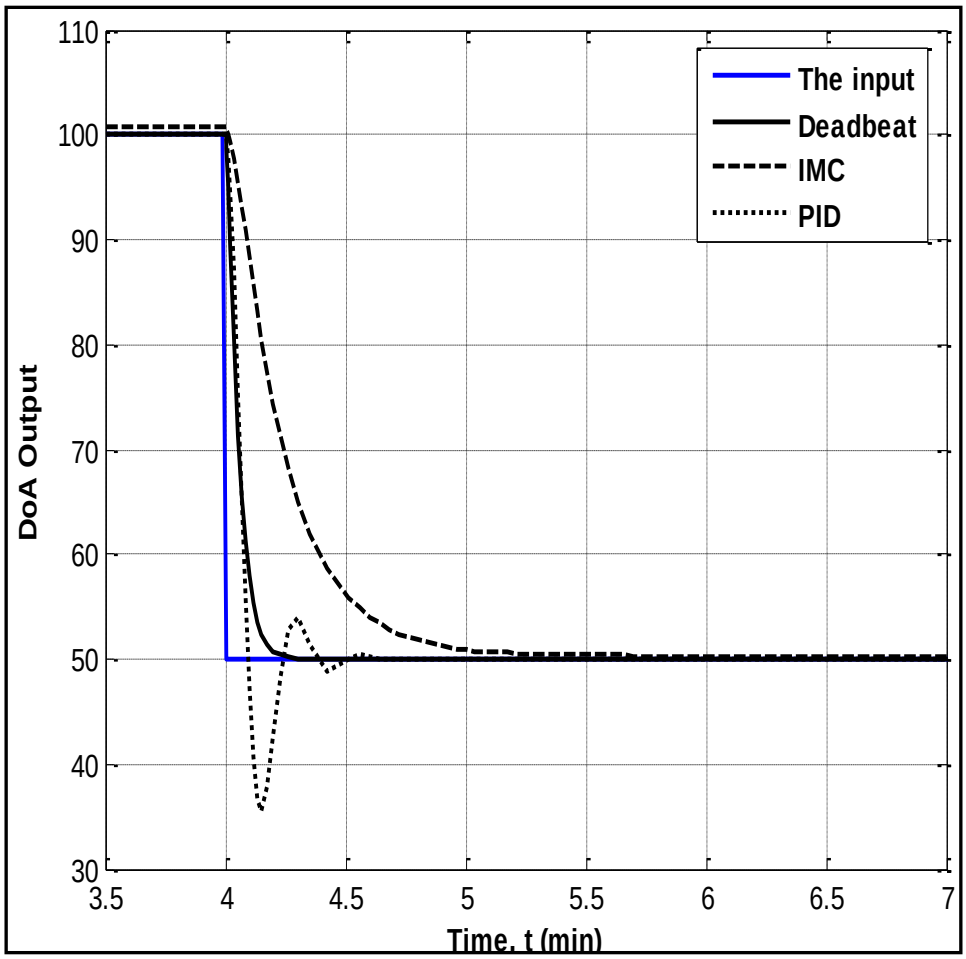

Figure 6.8: Comparison of the performance of the deadbeat with IMC and PID controllers'

Figures 6.6 and 6.7 show the responses of DoA system in different situations, in other words the values of K are changing from 1 until the system reaches a better response. For example, in Figure 6.7 K equals 2, 2.5 and 7.23. It is clear that all the responses settle and reach the desired positions with the time frames. While, there is overshoot, the system responses still meet with all the requirements and specifications.

Figure 6.8 shows the response of a traditional PID control for DoA. The parameters of the PID controller for DoA are K_p =1000, K_i= 10 and K_d=32. Comparing Figure 6.7 and 6.8, it is clear that the robust control performance is far better that the traditional control.

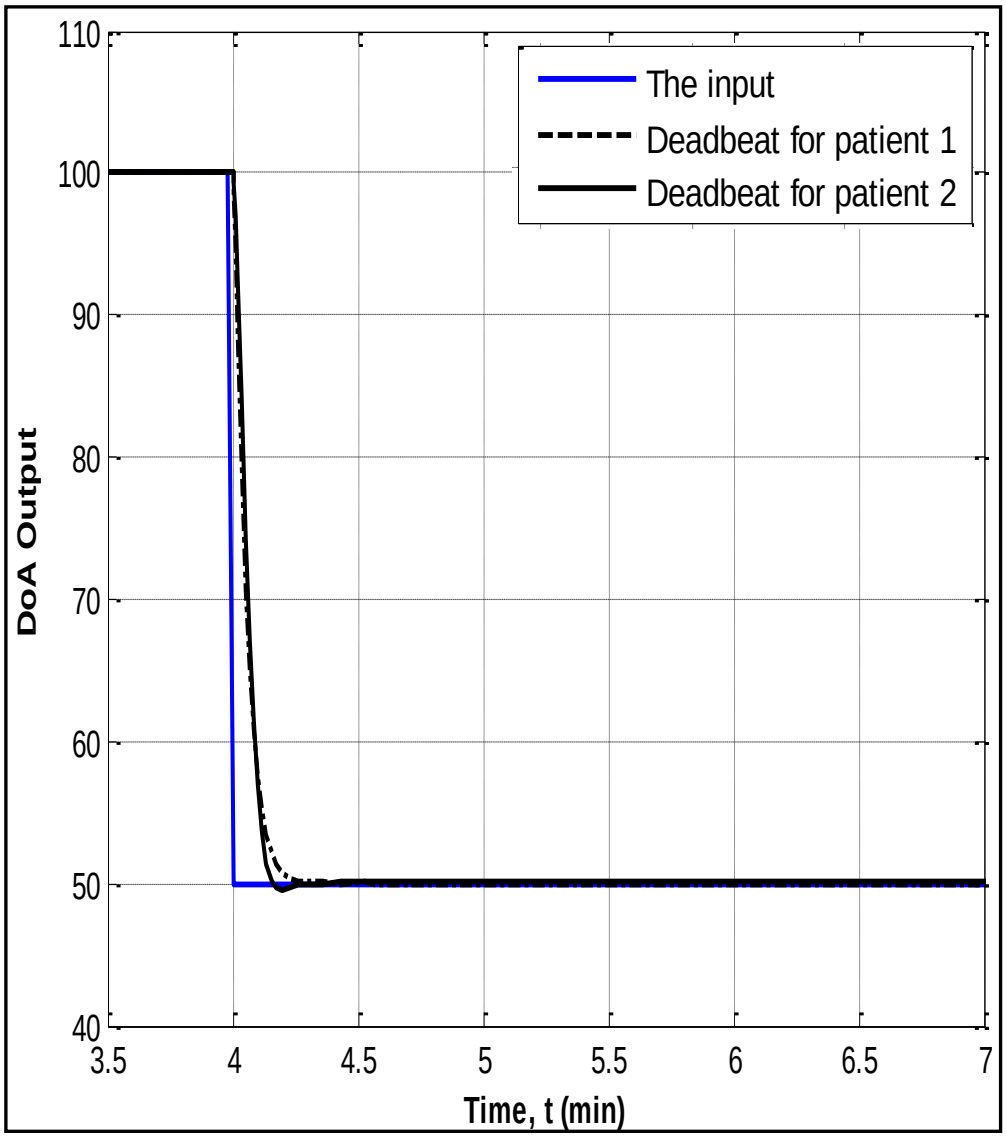

Figure 6.9: DoA deadbeat control response for different patients

Figure 6.9 shows the response of the deadbeat control response for different patients for DoA. Comparing Figure 6.8 and 6.9, it is also clear that the robust control

performance is much better that the IMC, where the settling time is approximately eight minutes for IMC and about 4.3 minutes for the robust deadbeat control.

The deadbeat design can tolerate system parameter changes to about 40% without degrading system performance. Figure 6.10 shows the responses after changing the model parameters form 10% to 20%, 30%, 40% and 50%. As a result the system's response remains almost unchanged when all the plant parameters vary by as much as 40%. The response of the system with no plant variations and then with 40% of plant parameter variations, is acceptable.

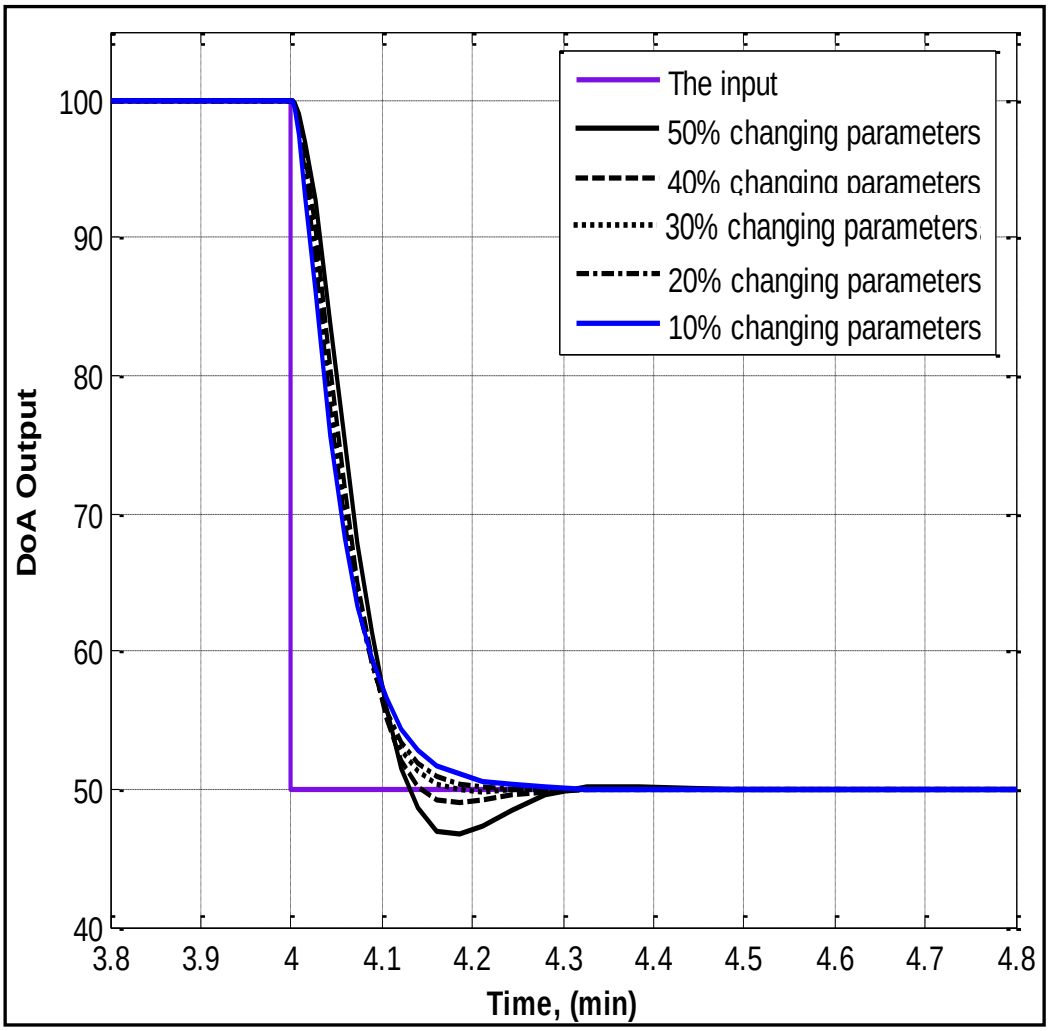

Figure 6.10: DoA deadbeat control response for changing patient parameters

6.6 Conclusions

This study investigated a PID-based robust deadbeat control technique in DoA control. The technique was originally designed to suppress system parameter uncertainties. We applied this technique to accommodate the inter-patient differences for DoA control

The proposed method was implemented and evaluated in simulation using realistic data. The results are compared with the results obtained using two other methods. The results show that the proposed robust deadbeat control scheme performs better both in overshoot/undershoot and settling time. The system settling time has been reduced to 1.5 minutes and the over and undershoot has been shorted about 15%. To investigate the robust capacity, we have changed the system parameters from 10% to 20%, 30 %, 40% and 50%. The results show that the proposed method can tolerate about a 40% change in parameters. In addition, the robust deadbeat control scheme is easier to design and does not need any complicated math calculations except the normalisation of the coefficients table.

CHAPTER 7

MODEL PREDICTIVE CONTROL OF DOA

7.1 Model Predictive Control Technique

Model Predictive Control (MPC) has been recognised, in process control, as a proven technology capable of dealing with a wide range of multivariable constrained control problems. Nevertheless, most industrial controllers are based on linear internal models, which limit their applicability.

This chapter demonstrates the control of hypnosis using Model Predictive Controller and compares its performance with PID and IMC approaches.

In clinical anaesthesia, automatic regulation in a closed-loop control of infusion of drugs, has been shown to provide more benefits when compared to manual administration (Abdulla & Wen, 2011; Abdulla & Wen, Peng 2011; De Keyser & Ionescu 2003; Gentilini, et al. 2001; Sreenivas, Lakshminarayanan & Rangaiah

2007). A well-designed model predictive control system can avoid both the over-dosage and under-dosage of drugs. Closed-loop control minimizes drug consumption, intra-operative awareness and recovery times, thereby decreasing the cost of surgery and the cost of postoperative care. Overall, this improves the patient's safety during surgery and rehabilitation after the surgery.

Absalom et al. (2003) produced a closed-loop control system of anaesthesia that uses BIS as the control variable to automatically control the target blood concentration of Propofol (Target Controlled Infusion (TCI) system). The system was able to provide clinically sufficient anaesthesia in all patients, with enhanced accuracy of control. There was a tendency for more accurate control in those patients in whom the control algorithm incorporated effect-site steering (Absalom & Kenny 2003; Engdahl et al. 1998). A method and an algorithm are proposed for controlling the effect site concentration using a TCI method. The method limits the peak plasma concentration, thereby slowing the start of anaesthetic drug effect but potentially improving side effects. Simulation is used to observe the delay in time to peak effect for five types of anaesthetic drug when the peak plasma concentration is limited by the algorithm; the control system was evaluated in 30 patient cases. This study clearly suggests the desirability of individual tuning of the controller parameters.

A method for an enhanced tuning of the PID controller parameters to the patient's individual dynamics was presented by Mendonca & Lago (Mendonca & Lago 1998). Auditory Evoked Potentials (AEP) has been reported to accomplish many requirements for measurement of the level of anaesthesia. A development has been made to this system to obtain a single index which presents the morphology of the

AEP and uses this index as the input signal for closed-loop anaesthesia during surgery in patients who did not receive neuromuscular blocking drugs (Kenny & Mantzaridis 1999). A robust control of depth of anaesthesia was developed by Dumont et al. (2009) to design both robust and PID controllers based on fractional calculus to control the hypnotic state of anaesthesia with intravenous management of Propofol (Dumont, Martinez & Ansermino 2009). The objectives of these controllers are considered to compensate for the patient's inherent drug response variability, to accomplish good output disturbance rejection, and to achieve good tracking to set point response (Ejaz & Jiann-Shiou 2004). The infusion and the drug effect are represented by the pharmacokinetic and pharmacodynamics models (Bressan et al. 2007).

A model based on a compartmental approach is used. In each compartment, the drug concentration is homogeneous and there are exchanges between compartments. A three compartments model is used, in which the main compartment represents intravascular blood (blood within arteries and veins) and highly irrigated organs (such as heart, brain, liver and kidney). The two other compartments represent muscles, fat and other organs or tissues. The PK consists of a 3-compartment model shown in Figure 7.1.

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{c}_e \end{bmatrix} = \begin{bmatrix} -k_{10} - k_{12} - k_{13} & k_{21} & k_{31} & 0 \\ k_{12} & -k_{21} & 0 & 0 \\ k_{13} & 0 & -k_{31} & 0 \\ k_{e0} & 0 & 0 & -k_{e0} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ c_e \end{bmatrix} + \begin{bmatrix} B_2 \\ 0 \\ 0 \\ 0 \end{bmatrix} u \qquad (7.1)$$

$$x(k+1) = Ax(k) + Bu(k) \qquad (7.2)$$

$$y(k) = C_y\, x(k) \tag{7.3}$$

$$C_y = [C_2\ 0\ 0\ 0] \tag{7.4}$$

where x_1 represents the amount of drug in the central compartment, x_2 and x_3 denote the amount of the drug in compartments two and three, respectively. Also B_2 is equal to $\frac{10^4}{3600}$ and C_2 is equal to $\frac{1}{1\times v_1}$. The constants k_{ij} represent the transfer rate of the drug from the i th compartment to the j th compartment. The constant k_{10} is the rate of the drug metabolism and u is the infusion rate of the anaesthetic drug into the central compartment.

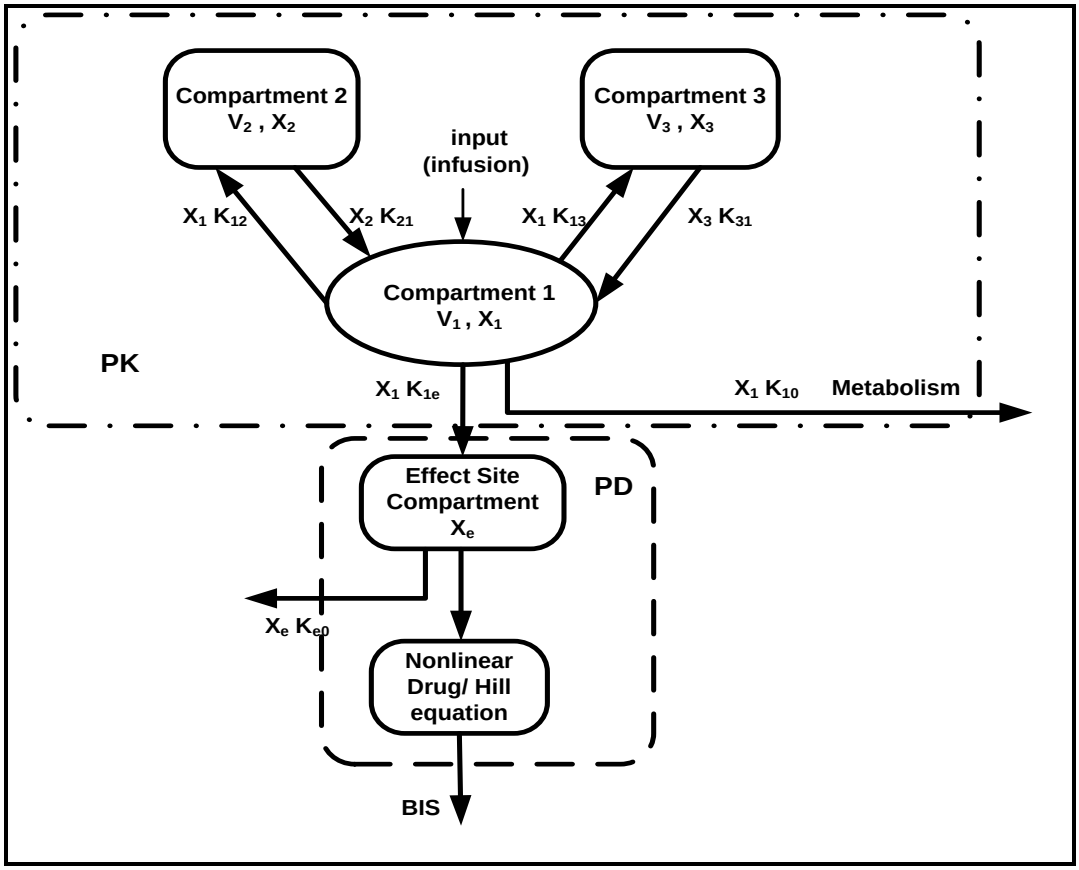

Figure 7.1: Compartmental model of the patient

The pharmacodynamics is characterized by a low-pass filter related to the central compartment concentration C_p in blood:

$$C_e = \dot{x}_e = -k_{e0}x_e + k_{1e}x_1 \tag{7.5}$$

where k_{e0} and k_{1e} are constants and x_e is the amount of drug in the effect compartment and x_1 is the plasma Propofol and and Remifentanil concentrations.

$$C_e(s) = \frac{k_{e0}}{(s + k_{e0})} C_p(s) \tag{7.6}$$

where k_{e0} is the inverse of the effect-site compartment time constant and EC_{50} is the half-maximal effective concentration. γ is a steepness of the concentration response relation.

The effect-site concentration is related to depth of anaesthesia (DoA) as (Hill equation) (Munson & Bowers 1967):

$$E(t) = E_o - E_{max}\left[\frac{{C_e}^{\gamma}}{EC_{50}^{\gamma} + {C_e}^{\gamma}}\right] \tag{7.7}$$

where E_0 represents the baseline value (conscious state without Propofol), which is typically set to 100; E_{max} denotes the maximum effect achieved by the drug infusion; EC_{50} is the drug concentration at half maximal effect and denotes the patient's sensitivity to the drug; and γ determines the steepness of the static nonlinearity.

7.2 Model Predictive Control Design

The fundamental objective of MPC as shown in Figure 7.2 is to determine the sequence of M future control policy (manipulated variable changes) so that the sequence of P predicted values (output variables) has minimal set-point tracking error (Shridhar & Cooper 1997). The main purpose of the non-linear model predictive control is to find the future optimal drug infusion sequence in order to minimize a function based on a desired output trajectory over a prediction horizon to adjust the amount of medication given to improve recovery from anaesthesia (Yelneedi, Lakshminarayanan & Rangaiah 2009). The cost function is the integral over the squares of the residuals between the models predicted outputs y and the set point values r over the prediction time.

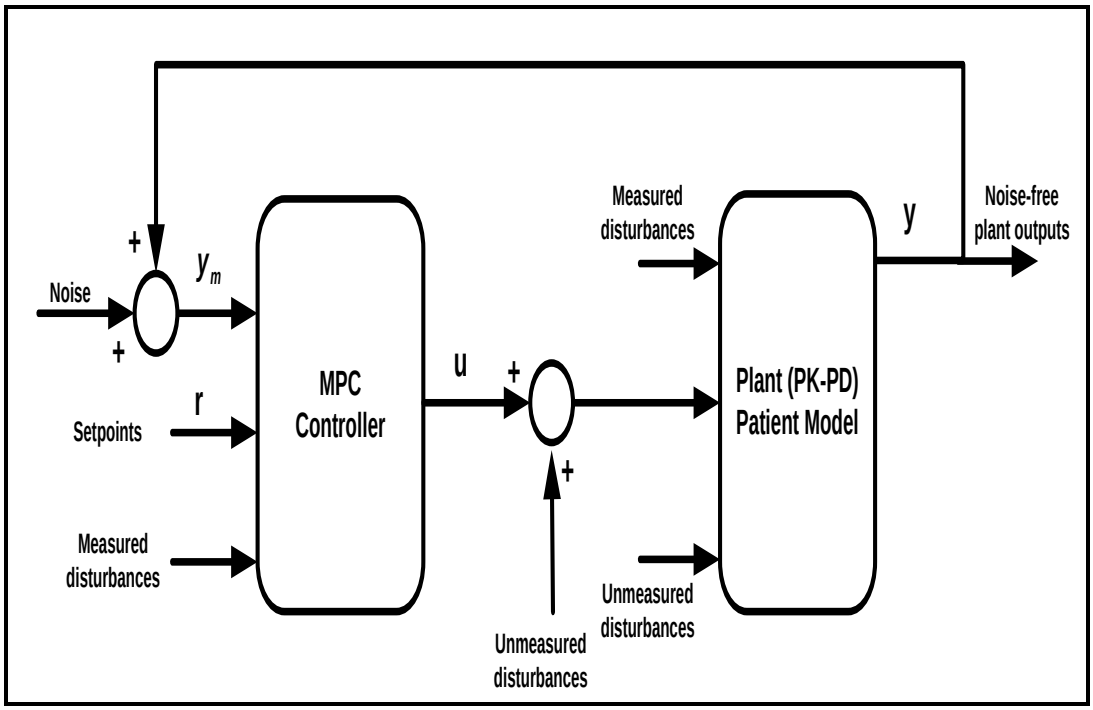

Figure 7.2: Model predictive control scheme

where, r is the set-point of the target for the BIS, u is the controlled variable, the Propofol infusion rate ($u = r^{prop}$) given in [mL/h], y is the output, the DoA level given in [%], d is the disturbance ($d = c_e^{remi}$), the Remifentanil effect concentration given in [µg/mL], and $d = c_e^{prop}$ is the Propofol effect concentration given in [µg/mL].

Model Predictive Control (MPC) is currently the most accepted method for handling disturbances predicting and estimating changes (Jonker et al. 2005). MPC plays an important role in solving such complex problems. The main elements of the method are plant model, constraints and objective function, as shown in Figure 7.3. The objective function is evaluated and the selection of controller is repeated until the optimum is obtained (Bequette 2007).

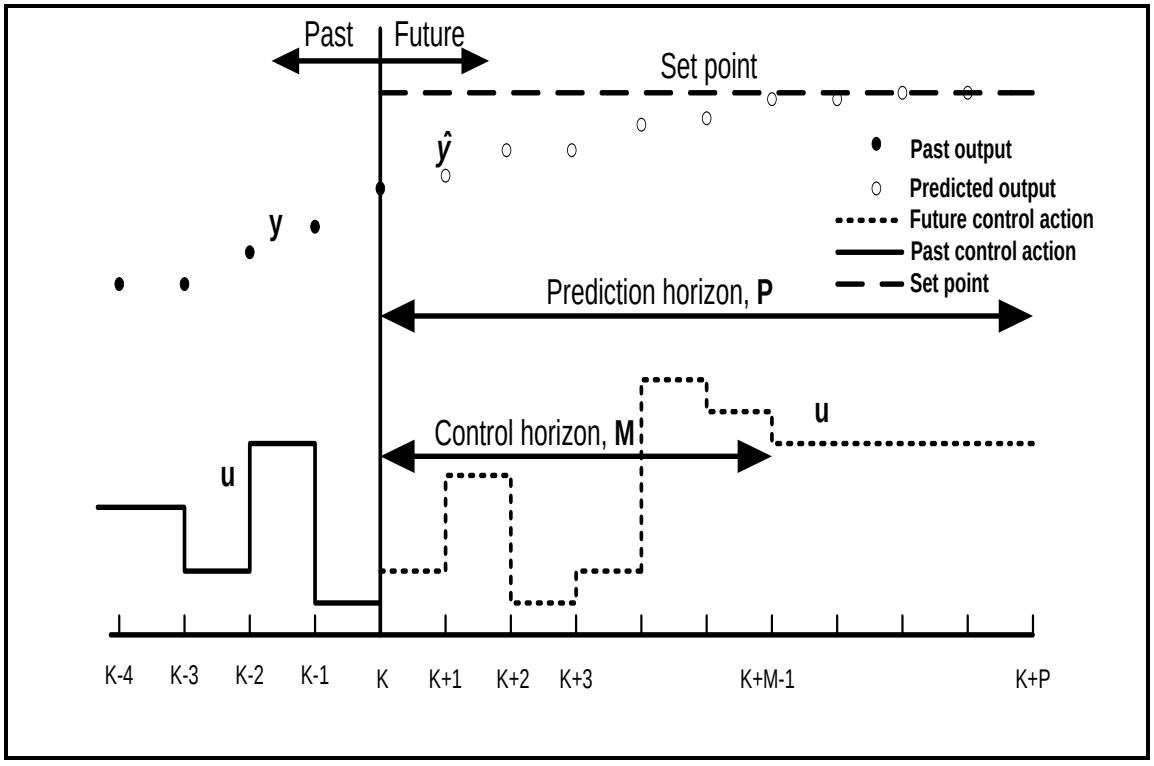

Figure 7.3: The basic concept of model predictive control

The technique requires solution of optimization problem at every sampling time, other constraints on the drug infusion can be added, such as, that the drugs (propofol) rate are to remain constant during the last numbers of steps. A linear or quadratic cost functions will be used. Stability results are obtained on the same idea as made for linear systems. One or several of the following assumptions are made, terminal equality constraints, terminal cost function, terminal constraint set and dual mode control (infinite horizon): begin with MPC with a terminal constraint set, switch then to a stabilizing linear controller when the region of attraction of the linear controller is reached (Weber et al. 2004). Generally, an MPC algorithm consists of applying a control sequence that minimizes a multistage cost function. A typical formulation is

$$J = \sum_{i=k+1}^{k+P} e_i^T Q e_i + \sum_{i=k}^{k+M-1} \Delta u_i^T R \Delta u_i \qquad (7.8)$$

Subject to:

$$u_{min} \leq u_i \leq u_{max} \quad (\text{for } i = k, k+1, k+2, \dots\dots\dots, k+M-1)$$
$$u_{i-1} - \Delta u_{max} \leq u_i \leq u_{i-1} + \Delta u_{max} \quad (\text{for } i = k, k+1, k+2, \dots\dots\dots, k+M-1)$$

where, M and P as the lengths of the prediction and control horizons, Q and R are the weighting matrices for both BIS and input rate respectively.

These Q and R can be used to tune the MPC controller to achieve the desired value between output performance and manipulated variable movement.

MPC controllers are based on an optimal control problem. Therefore, the weights used in the cost function should be determined. Another cost function for the MPC

block in MATLAB (see equation (7.9)) has been used to improve the drug infusion during surgery (Cardoso & Lemos 2008).

$$J = (Y - R)^T W_y^2 (Y - R) + \left(U - U^{desired}\right)^T W_u^2 \left(U - U^{desired}\right) + \Delta U^T W_{\Delta u}^2 \Delta U + \rho_\varepsilon \varepsilon^2 \quad (7.9)$$

where, W_u is a diagonal matrix representing the input weight, $W_{\Delta u}$ is a diagonal matrix representing the input rate weight, W_y is a diagonal matrix representing the output weight, $U = [u_t \cdots u_{t+M-1}]^T$ is the vector of values of the control signal over the control horizon, $U^{target} = [u_t^{target} \cdots u_{t+M-1}^{target}]^T$ is the vector of values of the desired control signal over the control horizon, $\Delta U = [\Delta u_t \cdots \Delta u_{t+M-1}]^T$ is the vector of values of the rate of the control signal over the control horizon, $Y = [y_{t+1} \cdots y_{t+P}]^T$ is the vector of values of the output over the prediction horizon, $R = [r_{t+1} \cdots r_{t+P}]^T$ is the vector of values of the reference over the prediction horizon, ρ_ε is the weight factor on the slack variable (used to penalize the violation of the constraints), and ε is the slack variable, a variable to turn the inequality into an equation, it allows the constraints to be violated by a certain amount.

7.2.1 Constraints

The range of DoA signal is between 0 and 100% (initial signal is about 97.7%) and the Propofol infusion must be at a positive rate (a negative rate would mean that propofol was being taken from the patient). These constraints are summed as shown in Table 7.1.

Table 7.1: Model predictive controller constraints

Variables	Minimum	Maximum
$u\ [\frac{mL}{h}]$	0	∞
$\frac{du}{dt}\ [\frac{mL}{hs}]$	$-\infty$	$+\infty$
$DoA\ [\%]$	0	100

In reality, these are the basic constraints. The maximum drug infusion rate and the changes in the medication infusion rate are constrained by the apparatus and equipment, but these bounds are very high and are never reached in practice.

7.2.2 Time horizons

The prediction horizon P has been chosen based on open-loop settling time, whereas control horizon M is chosen based on the value between faster response (large value of M) and robustness (small value of M). Therefore, the chosen value for M is very small, compared to P. To reject the disturbances that are due to patient-model mismatch, the patient model is augmented by the output disturbance model, which is an integrator that is driven by white noise.

The MPC parameters are output (BIS) weight, Q = 1; input rate (Propofol) weight, R = 0.8; prediction (output) horizon, P = 30; and control (input) horizon, M =3. These parameters have been chosen by using direct search optimization for hypnosis regulation.

7.2.3 The simulation model of MPC

The main tuning parameters are the control and prediction horizons (M and P) and the weight applied to manipulated and control variables.

The prediction horizon determines the amount of predictions that are used in the optimisation calculations. Increasing the prediction horizon results in more conservative control action that has a stabilising effect, also increases the computional efforts (Yelneedi, Samavedham & Rangaiah 2009). A very large predication horizon recommended only for a very good model and if feedback is limited.

The control horizon determines the number of future control actions that are calculated in the optimisation step to minimise the predicted errors. A large number for the control horizon, relatively to the prediction horizon, tends to too much control actions, but small value for control horizon leads to a robust controller.

The model predictive control simulation design shown in Figure 7.4, the patient model has been used to estimate the value of the output variable BIS. The difference between the measured BIS from the process model and the model output, serves as the feedback signal to the prediction part. With this model output and input variable, the predction part estimates the future values of the output BIS. Base on the predicted BIS values, the MPC controller calculates the future input moves of which only first input move is implemented by the controller at current sampling instant.

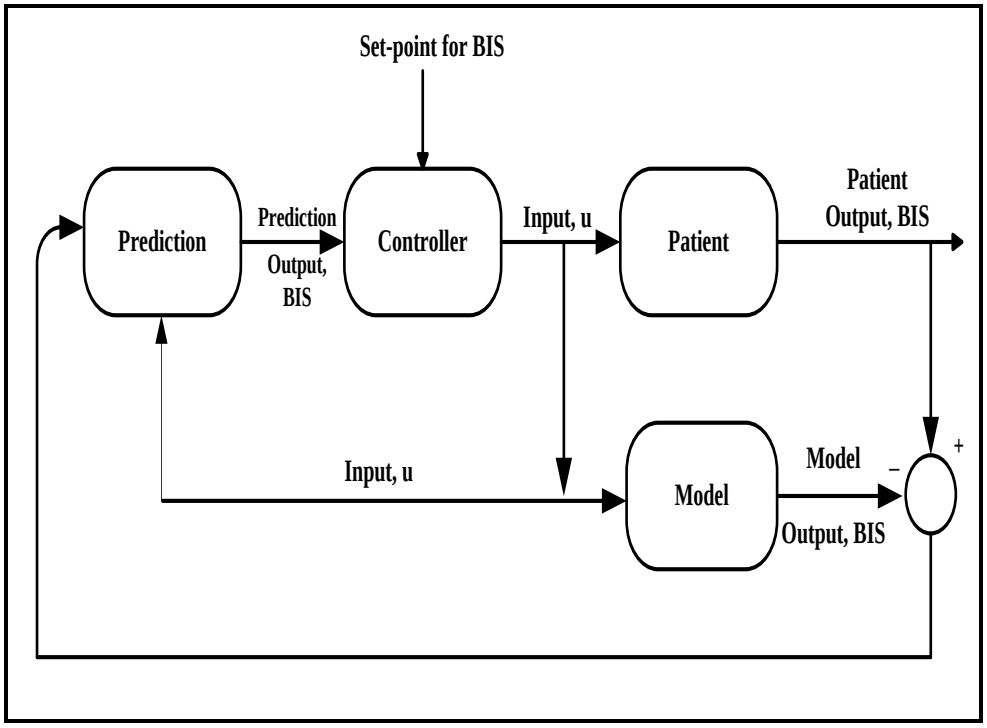

Figure 7.4: The model predictive control simulation design

7.3 Results and discussion

A Model Predictive Control system of Propofol and Remifentanil is constructed. The time that the BIS reaches the range of 50 ± 10, is called the settling time for the BIS during general anaesthesia. The specifications of the MPC system for the settling time range was between 5 and 10 mintues and the robutness was stable for all parameters obtained in the simulation results and is shown in Figure 7.5.

The target value of BIS is between 60 and 40. Figure 7.5 shows a simulation result for a subject with the nominal parameters. The MPC system can maintain BIS at the relevant target levels and the settling time is within ten minutes.

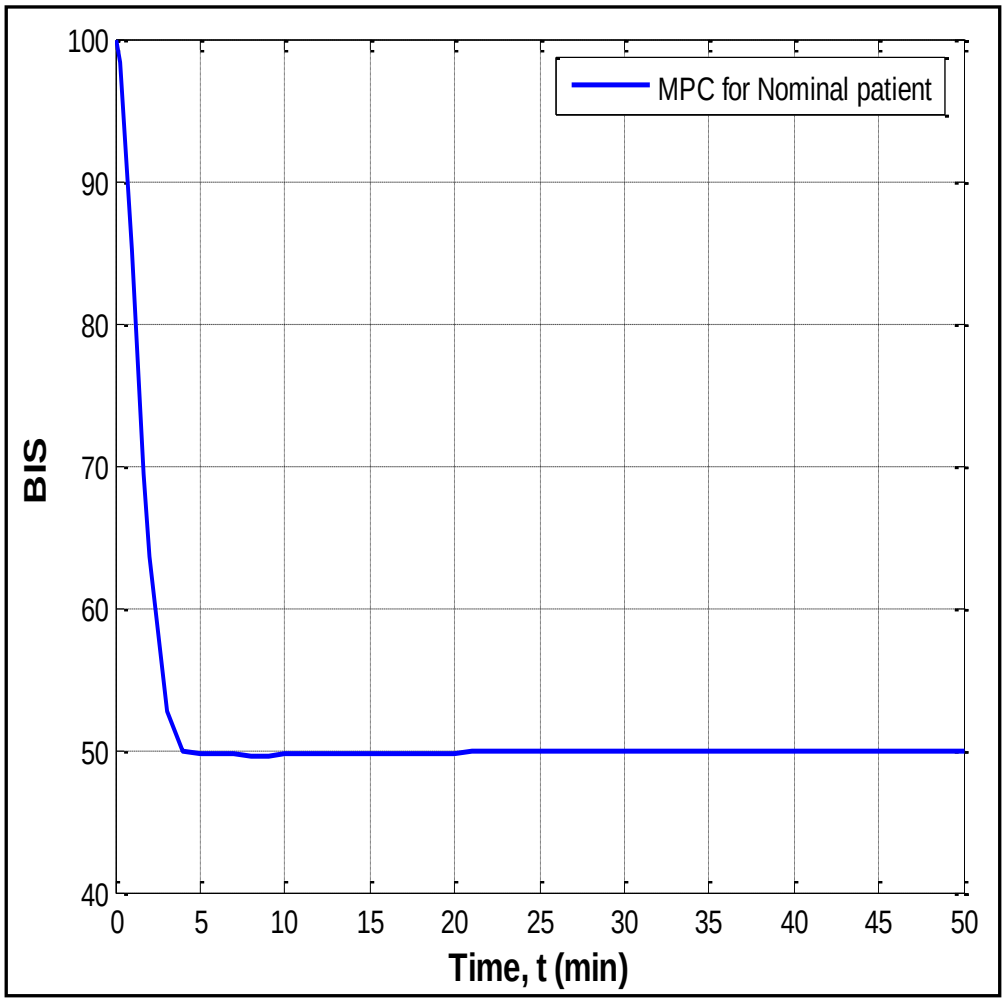

Figure 7.5: The performance of the MPC for nominal patient

The predicted plasma Propofol concentration (C_p^{prop}) has to be between 0.5 µg/ml and 5 µg/ml because it is the clinically accepted range (Absalom, Sutcliffe & Kenny 2002) that is not measured but estimated using the nominal patient model.

The manipulated variables u (propofol infusion rate) is constrained between 0 and 20 $mg/kg/hr$ (Furutani et al. 2005; Sawaguchi et al. 2008).

The tuning of the MPC design for the nominal patient's data for DoA parameters shown in Table 7.2. The MPC tuning parameters are M, and P, the input horizon and the prediction horizon respectively; Q and R, weighting coefficient for BIS and the weighting coefficient for the Propofol rate respectively. MPC controller performance for different tuning weights on the output variables and input variable rates for insensitive patients are shown in Figure 7.6.

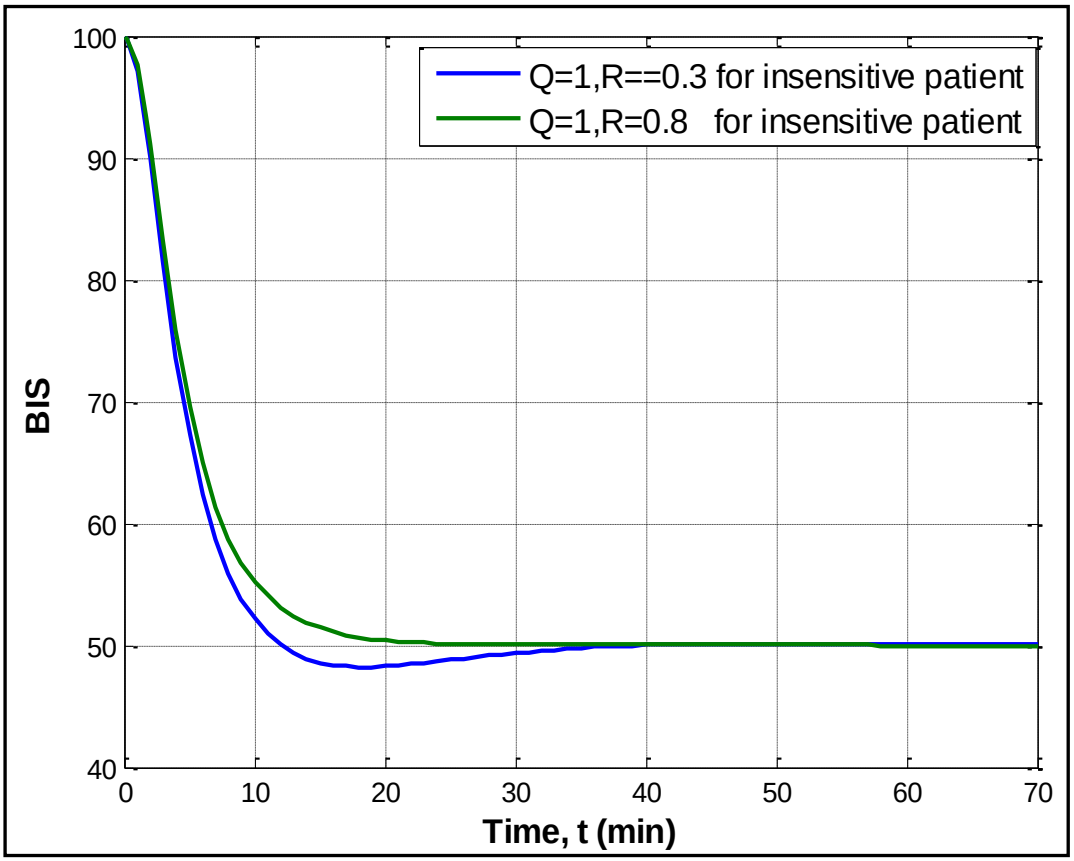

Figure 7.6: MPC controller performance for different R and Q weights

Table 7.2: Nominal patient's data for DoA parameters (Marsh et al. 1991; Minto, Schnider & Shafer 1997)

Variable	**Default value**	**Unit**
v_c	0.228	[L/kg]
k_{10}	0.119	$[min^{-1}]$
k_{12}	0.112	$[min^{-1}]$
k_{13}	0.0419	$[min^{-1}]$
k_{21}	0.055	$[min^{-1}]$
k_{31}	0.0033	$[min^{-1}]$
k_{e0}	0.25	$[min^{-1}]$
EC_{50}^{remi}	11.20	[µg/mL]
EC_{50}^{prop}	2.65	[µg/mL]
E_0	97.7	[%]
γ	2.561	

The performance of MPC, IMC and PID for sensitive patients for the set-point tracking during the surgery period is shown in Figure 7.7. These three controllers

(MPC, IMC and PID) are able to meet performance specifications in spite of the significant and reasonable variation in the model parameters such as inter-patient variability based on PK-PD model.

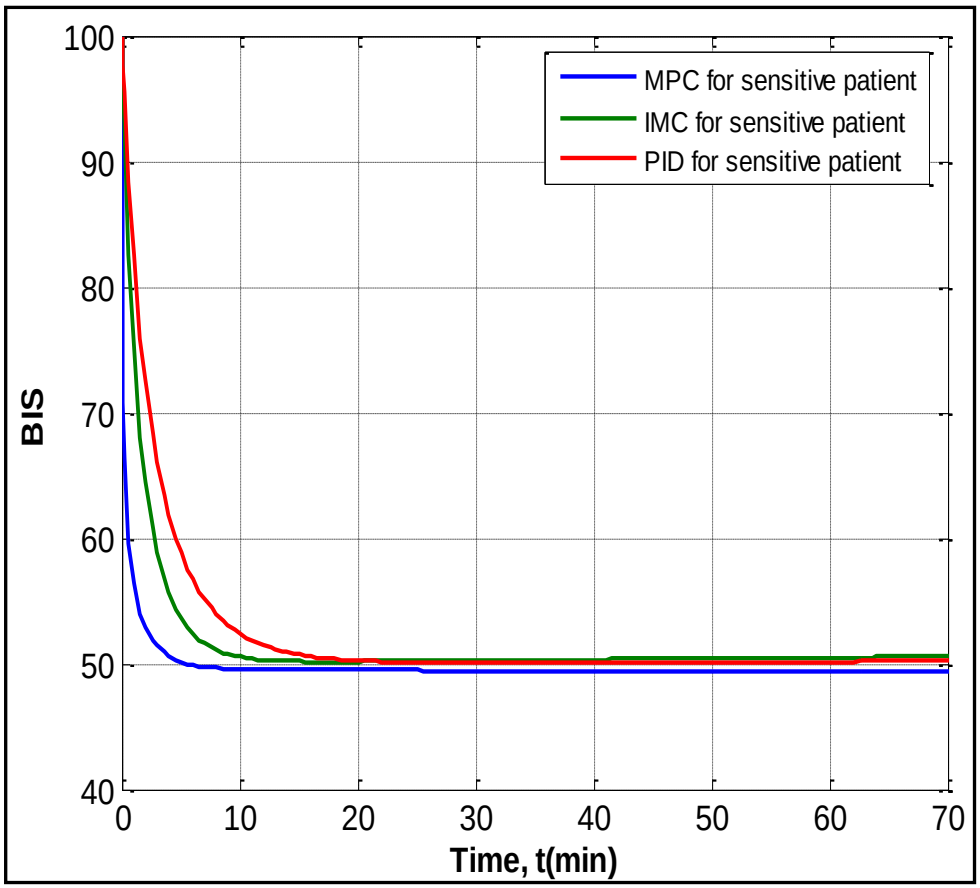

Figure 7.7: The performance of MPC, IMC and PID controllers for sensitive patient

There is a variation in PK (based on age and weight) and PD (patient's sensitivity to the drug) model parameters.This assumption is based on the inter-patient and intra-patient variability (Schnider et al. 1999). The PK variation is about 25% of the model's parameters. In addition, simulation studies showed that the variability in PD parameters have more impact on BIS than the variability in PK parameters (Schüttler & Ihmsen 2000).

The simulations results show that an insensitive patient requires relatively more Propofol and Remifentanil dosages and responds slowly to those drugs (as shown in Figure 7.8 for four different insensitive patients from Table 7.3 and 7.4).

Table 7.3: Patient PK-PD parameters for Propofol used in this study (Niño et al. 2009)

Patient	k_{10}	k_{12}	k_{21}	k_{13}	k_{31}	EC_{50}	k_{e0}	γ
1 (sensitive)	0.08925	0.084	0.06875	0.031425	0.004125	1.6	0.459	2.000
2	0.14875	0.112	0.06875	0.031425	0.002475	2.65	0.459	2.561
3	0.11900	0.112	0.05500	0.041900	0.003300	2.65	0.239	2.000
4	0.14875	0.140	0.04125	0.052375	0.004125	1.60	0.239	2.000
5	0.08925	0.084	0.06875	0.031425	0.002475	3.70	0.239	3.122
6 (Nominal)	0.11900	0.112	0.05500	0.041900	0.003300	2.65	0.349	2.561
7	0.14875	0.140	0.04125	0.052375	0.004125	3.70	0.349	2.561
8	0.11900	0.112	0.05500	0.04190	0.003300	2.65	0.239	2.000
9	0.08925	0.084	0.04125	0.052375	0.002475	3.70	0.239	3.122
10	0.08925	0.084	0.06875	0.031425	0.002475	3.70	0.239	3.122
11	0.11900	0.112	0.05500	0.041900	0.003300	2.65	0.239	2.561
12 (Insensitive)	0.14875	0.140	0.04125	0.052375	0.00247	3.70	0.239	3.122

Table 7.4: Patient PK-PD parameters for Remifentanil drug used in this study (Niño et al. 2009)

Patient	k_{10}	k_{12}	k_{21}	k_{13}	k_{31}	EC_{50}	k_{e0}	γ
1 (sensitive)	0.38175	0.2715	0.24375	0.00975	0.0175	7.840	0.6708	1.757
2	0.50900	0.3620	0.24375	0.01625	0.0105	7.840	0.6708	1.757
3	0.63625	0.2715	0.24375	0.01300	0.0140	7.840	0.6708	1.757
4	0.63625	0.2715	0.24375	0.01300	0.0140	7.840	0.6708	1.757
5	0.63625	0.2715	0.24375	0.01300	0.0140	7.840	0.6708	1.757
6 (Nominal)	0.50900	0.3620	0.19500	0.01300	0.0140	11.20	0.5160	2.510
7	0.50900	0.3620	0.19500	0.01300	0.0140	11.20	0.5160	2.510
8	0.50900	0.3620	0.14625	0.00975	0.0140	14.56	0.5160	1.757
9	0.63625	0.2715	0.14625	0.01625	0.0175	11.20	0.5160	1.757
10	0.38175	0.3620	0.19500	0.00975	0.0105	11.20	0.3612	1.757
11	0.50900	0.2715	0.14625	0.00975	0.0105	14.56	0.3612	2.510
12 (Insensitive)	0.63625	0.4525	0.14625	0.01625	0.0105	14.56	0.3612	3.263

Based on the PD parameters, changing the results shows that the higher EC_{50} indicates the need for more Propofol and Remifentanil drugs to get the same hypnosis and analgesia levels. Also higher γ (3.122) indicates higher non-linearity, and lower k_{e0} (0.239) represents a slowness in response.

A sensitive patient requires less drug dosage to get the same hypnosis and analgesia levels. In PD parameters, lower EC_{50} indicates that less Propofol and Remifentanil are required to get the same level of hypnosis and analgesia. The lower amount of γ,

represents weak non-linearity in the system response. Higher amount of k_{e0} indicates a quicker response.

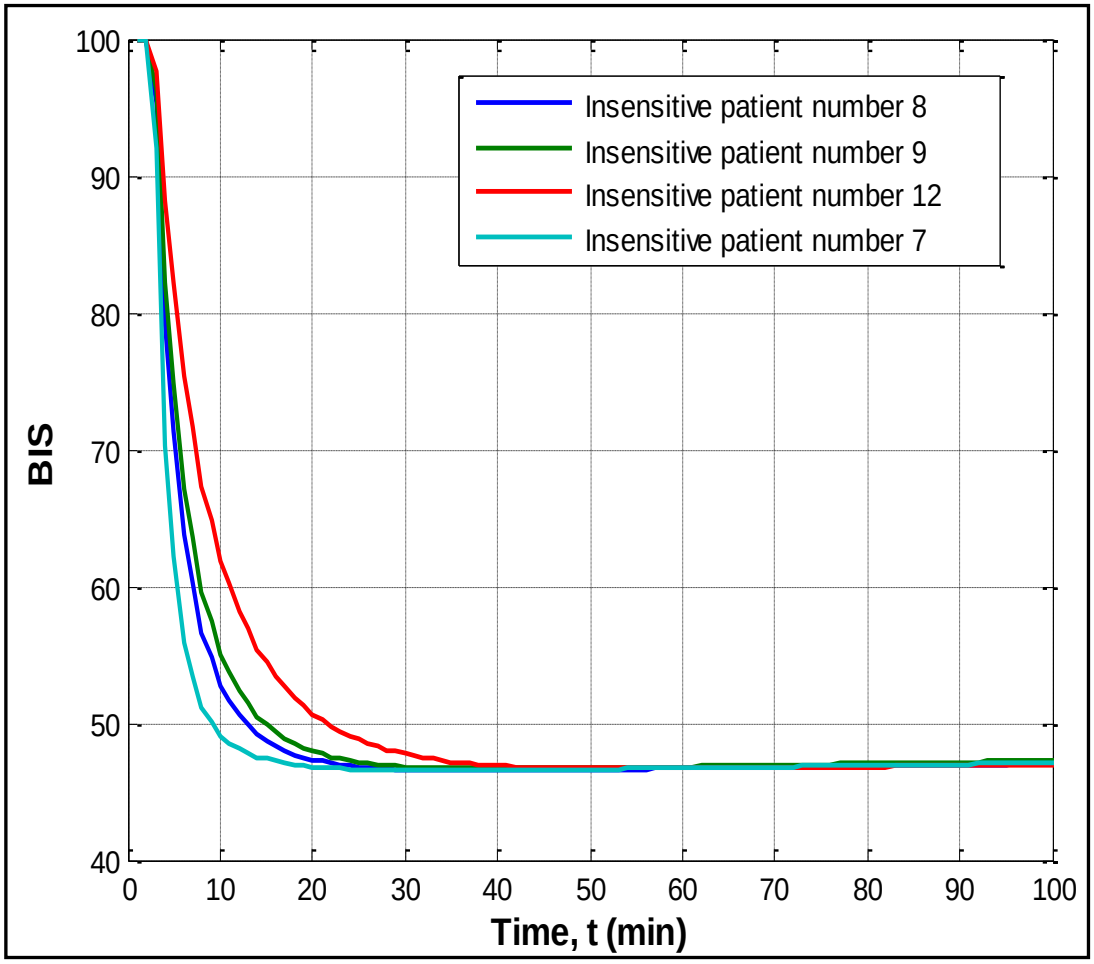

Figure 7.8: The performance of MPC controllers for four insensitive patients

Figures 7.9 and 7.10 show the performance of the MPC for sensitive patient is faster, drug usage is less, and that the response for the insensitive patient is sluggish and drug usage is high compared to the response of the nominal patient.

The performance of the three controllers (MPC, IMC and PID) is checked for the 12 patients, the insensitive, nominal and sensitive patients.

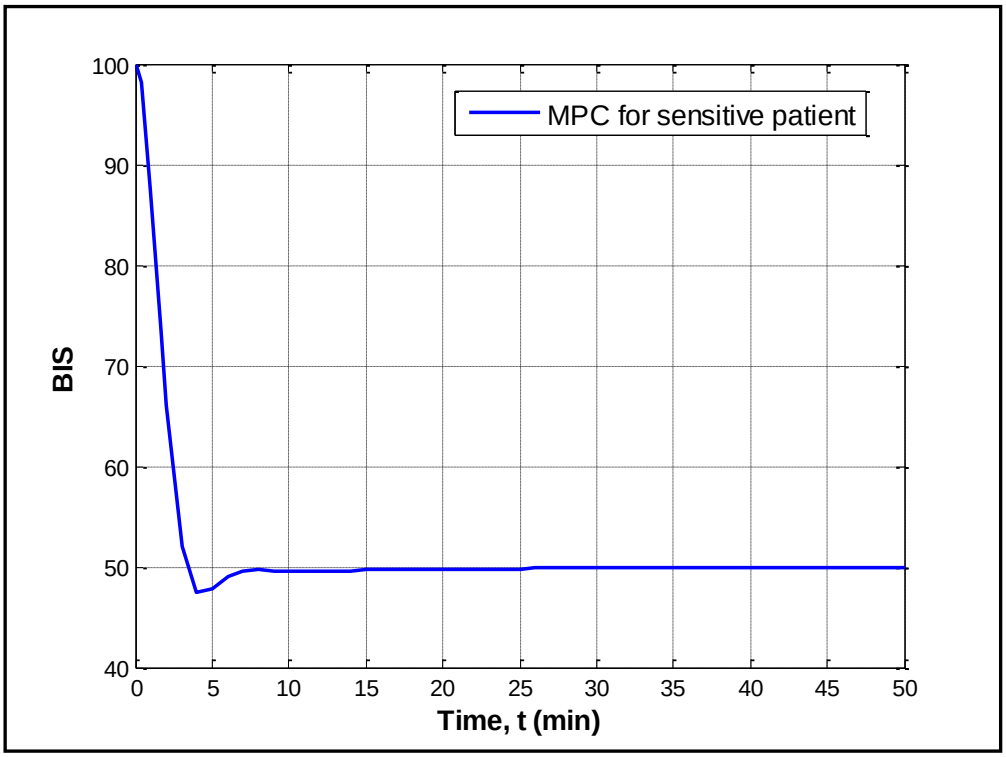

Figure 7.9: The performance of MPC controllers for sensitive patient number 2

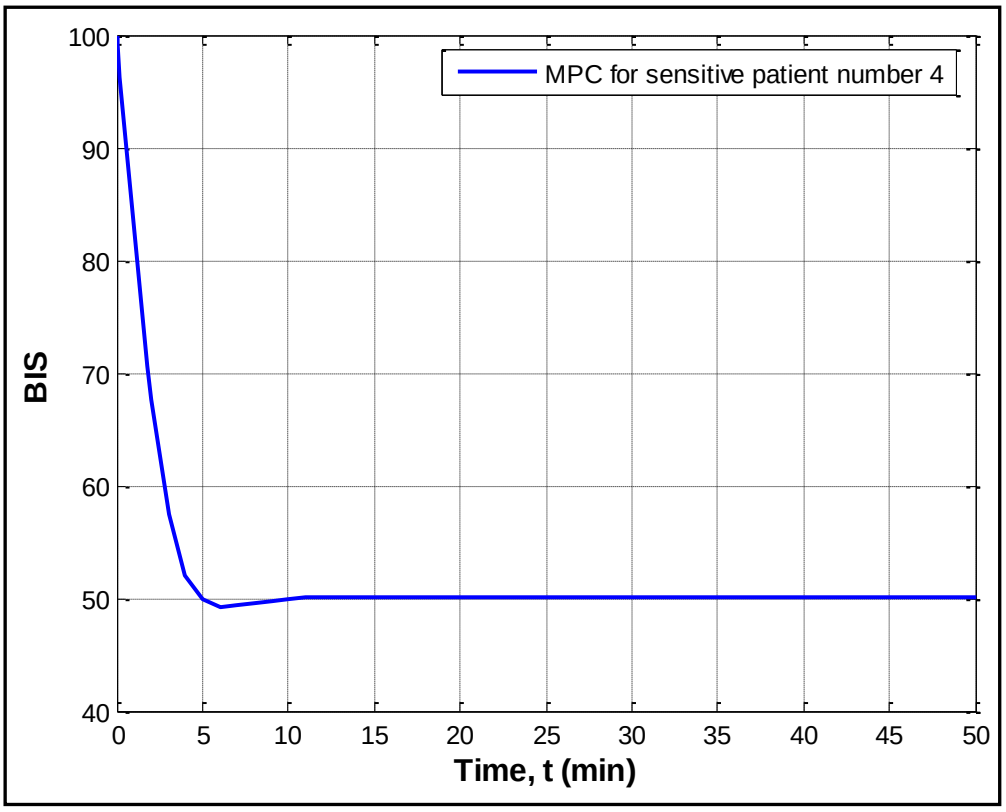

Figure 7.10: The performance of MPC controllers for sensitive patient number 4

The Simulink model structure can be seen in Figure 7.11.

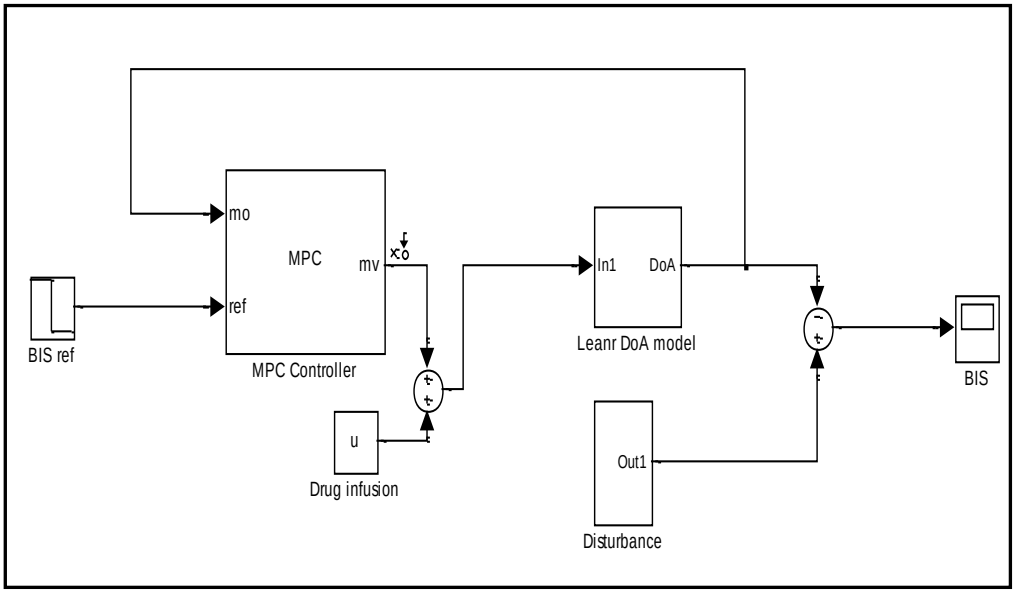

Figure 7.11: The Simulink model structure

Figure 7.12 depicts the responses of IMC and PID controllers for disturbances in the BIS signals for the insensitive patient. Figure 7.13 shows the MPC performance of a sensitive patient at a set point of 50 and the controller maintained the BIS within the operating range in spite of noise in the signal. It can clearly be concluded that the performance of the MPC is better than that of IMC and PID controllers. The average control effort with MPC is higher compared to IMC and PID controllers. At this point, larger disturbances cause higher valve movement leading to a higher control effort with MPC. These disturbance effects dominate the effect of noise in BIS signal which mostly affect the performance and control effort of IMC and PID compared to MPC.

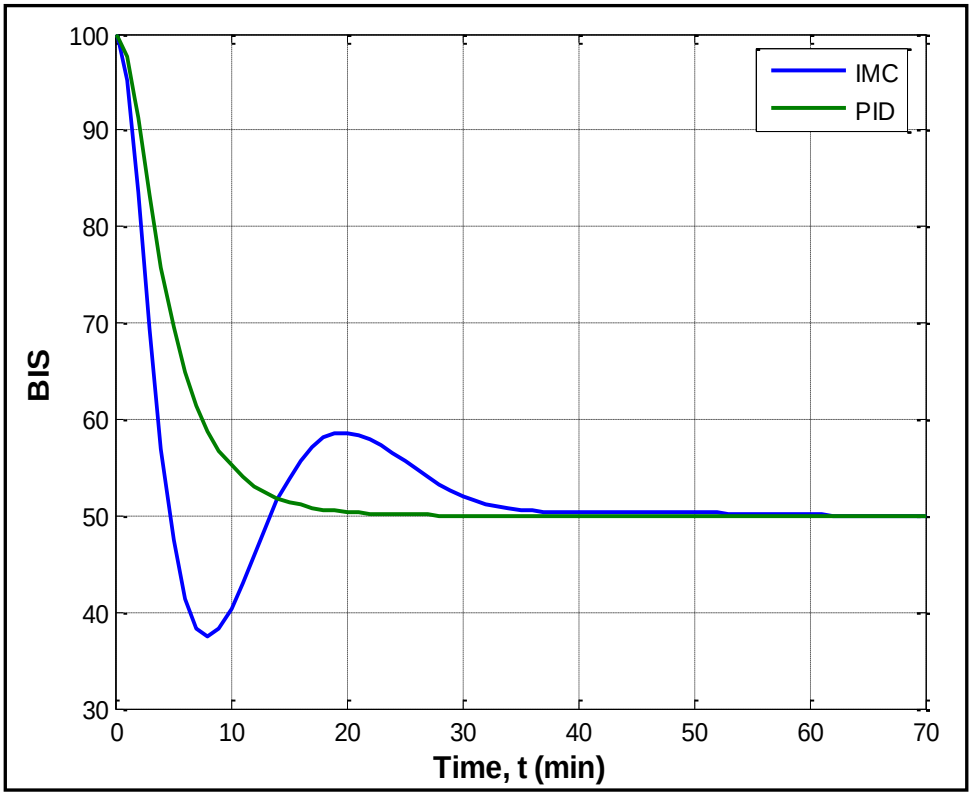

Figure 7.12: The performance of IMC and PID controllers for insensitive patient

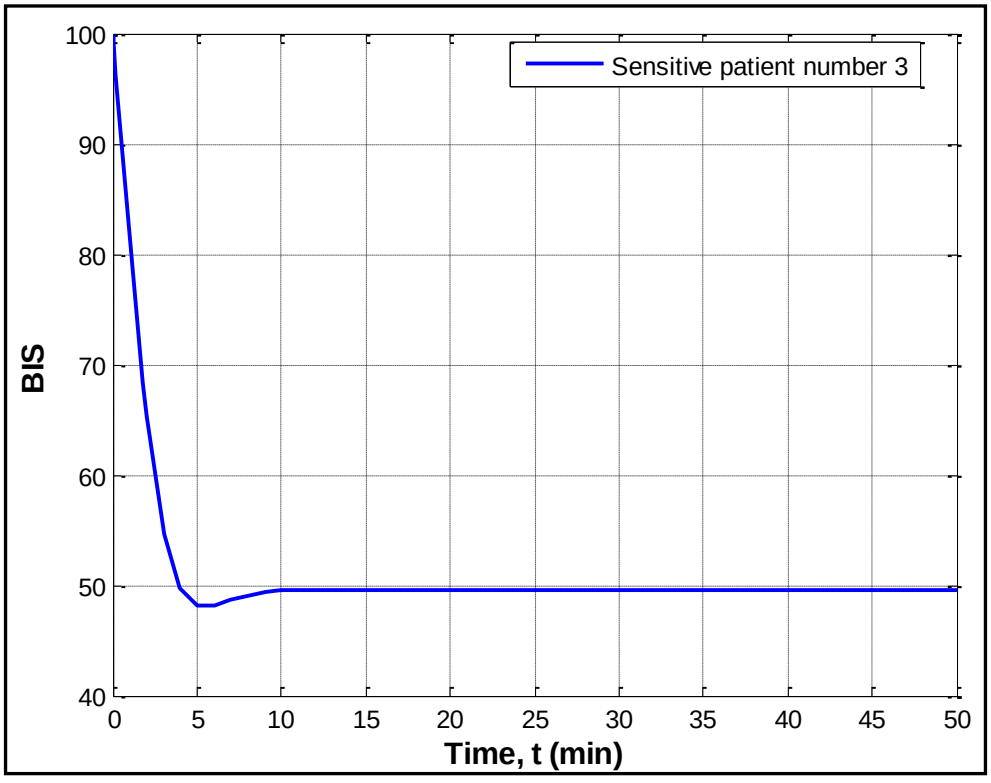

Figure 7.13: The performance of MPC controllers for sensitive patient number 3

7.4 Conclusions

The automatic induction of anaesthesia drugs has more advantages when compared to the manual administration of other drugs. In this chapter, a model predictive control strategy has been developed for automatic regulation of hypnosis and analgesia using BIS as controlled variables. The controllers were designed based on a nominal patient model, and then tested for their effectiveness, ability and robustness on 12 patient parameters covering sensitive to insensitive patients and operating conditions by the use of Simulink simulation. The results show that the MPC controller is capable of improving Propofol and Remifentanil inductions by 20 to 25% compared to PID controller, 8 to 10% compared to The IMC, and better robustness in set-point tracking and disturbance rejection when implemented on different patient parameters. In addition, the MPC control scheme is easier to design and does not need any complicated mathematical calculations.

CHAPTER 8

CONCLUSIONS AND FUTURE WORK

8.1 Review of Research

This dissertation described the contemporary developments of depth of anaesthesia control techniques and human body model. Five advanced controllers were proposed and thoroughly investigated for the closed-loop administration of hypnotics and analgesic medications. The results demonstrated their clinical feasibility on patients undergoing general anaesthesia.

Compartmental-based human body models aim to imitate drug distribution based on assumptions regarding drug binding, blood flow to the different body compartments and their respective volumes. These assumptions are based on measurements. The human body model parameters are generated by scaling the corresponding animal models. Mamillary compartmental models on the other hand are based on input-output data sequences. The synthesis of the advantages of both model concepts allows the description of a precise input-output behaviour. The derived model is adequately descriptive for control purposes.

8.2 General Conclusions

Chapter 3 studied the human models and the model development for hypnotic and analgesic. The description of the kinetics and dynamics of human body model were investigated. The pharmacokinetics and phrmacodynamics parameters variations in patient model to account for patient-model mismatch were also dicussed. Infusion of the anaesthetic to the detection of DoA using BIS includes considerable time-delays. The effects of the time-delay and time-delay model were analysed in this chapter. Two uncertainties in PK-PD modeling and their effects were investigated. The first uncertainty is caused by intra-patient variability, and the second is the uncertainty originating from inter-patient variability.

The IMC control of depth of anaesthesia using BIS as the controlled variable investigated in Chapter 4. The performance of the internal model controller was compared with that of the conventional PID controller. The IMC was found to be more robust to inter-patient variability and disturbances rejection compared to the PID controller. The proposed IMC control has no undershoot. The proposed IMC strategy was also found to be more robust to intra - patient variability.

Chapter 5 studied Smith Predictive Control and the effects of time-delay on depth of anaesthesia. This chapter investigated the impact of the time-delays of the patient and instrumentations such as the BIS monitor used in a closed-loop depth of anaesthesia control system, and proposed to apply the Smith Predictive Technique to identify and compensate the time-delay. The proposed method was evaluated using measured BIS signals in simulation. Extensive simulations were conducted using Simulink to test the performance of the SPC controller for robustness, set-point tracking, and

disturbance and noise rejection characteristics. The results showed that the proposed procedure improved the performance of the closed-loop system for reference tracking and overall stability. The proposed method also has about 15% less overshoot, is two minute shorter in settling time and is more robust to disturbances.

A robust deadbeat controller for patient model with uncertainties was investigated in Chapter 6. In this depth of anaesthesia control system, the model includes nonlinear parts. The proposed method applied a deadbeat control technique and developed a robust control method. The proposed robust control system with a deadbeat controller was evaluated in simulation. The results showed that the proposed robust deadbeat control scheme performs better both in overshoot/undershoot, and settling time. The system settling time is reduced to 1.5 minutes and the overshoot and undershoot are shortened about 15%. To investigate the robust capacity, we varied the system parameters from 10% to 20%, 30 %, 40% and 50%, and the results showed that the proposed method could tolerate upto 40% changes in model parameters. In addition, the robust deadbeat control scheme is easier to design and does not need any complicated mathmatical calculations except the normalisation of the coefficients table.

Chapter 7 investigated the depth of anaesthesia control system using model predictive control technique. We applied a predictive control technique and developed a robust controller. The controller was designed based on a nominal patient model, and then tested for effectiveness on 12 patients' parameters using Simulink. The MPC results were compared with that of a PID controller and with the internal model controller. The results showed that the proposed method reduced the

overshoot by about 20% compared to PID controller, reduced the settling time by about two minutes compared to the PID controller and about 10% compared to IMC controller (about one minute shorter) and that it was more robust to disturbances caused by parameter changes.

These simulations and evaluations performed in this study provide a guarantee on feedback control of depth of anaesthesia. In addition, the patient profiles developed and used in the current study would be valuable in future studies on depth of anaesthesia control.

Currently, the process of monitoring depth of anaesthesia and administration of a general anaesthetic during surgery is a closed-loop control system where the human is responsible for reasoning and action. Anaesthetists play the roles of controller and actuator by deciding on the amount of anaesthetic and when to administer it. On the other hand, the activity of monitoring is performed automatically by commercially available depth of anaesthesia monitors. Together they form a closed-loop control system. One of the main drawbacks in developing active drug delivery systems is the lack of accurate mathematical models for characterizing the dynamic behavior of drugs on physiological variables. System nonlinearities, model parameter variations from patient to patient, as well as parameter variations within the same patient under different conditions make it very challenging to develop models and effective control law architectures for active drug delivery systems. Even though control strategies based on fixed-gain linear control laws, adaptive linear control laws, and rule-based (fuzzy logic) control laws have been proposed in the literature, the complex and highly uncertain nature of patient response to multiple drugs renders

such strategies deficient in the face of large system variations and system nonlinearities.

This project is at the forefront of current international research, which addresses fundamental questions in the DoA assessment and control. The new models and control algorithms developed in this project is immediately useful in the development of new DoA control systems that have potential to greatly improve the comfort of patients, reduce the medical cost and avoid intraoperative awareness and all its consequences.

8.3 Future Work

A number of important topics on modeling and control of depth of anesthesia are outlined for further investigation in this project.

The depth of anaesthesia control requires the construction of an accurate model to describe a more realistic surgical scenario and to include additional inputs and outputs. Anaesthesia control can be developed using non-linear controllers to improve the patient's safety during surgery and rehabilitation after surgery.

Construction of multi-drug strategies is necessary, because sole control of hypnosis or analgesia will not provide the anesthetists with the full benefits of automatization.

This dissertation has emphasized the performance of several model-based predictive controllers for anesthesia regulation via simulations, but their clinical applicability and performance need to be established and demonstrated. For this reason, clinical

tests must be conducted before the developed control system can be used by the clinical team in the operating theatre. This important aspect must be investigated in detail in multi-disciplinary research studies.

REFERENCES

Abdulla, SA & Wen, P, 2011, 'Robust internal model control for depth of anaesthesia', *International Journal of Mechatronics and Automation*, vol. 1, no. 1, pp. 1-8.

Abdulla, SA & Wen, P, 2011, 'Depth of anaesthesia patient models and control', Proceeding of IEEE International Conference, Harbin, Heilongjiang, China, on 22-25 May, 2011, pp. 37-41.

Absalom, AR & Kenny, GNC 2003, 'Closed-loop control of propofol anaesthesia using bispectral indexTM: performance assessment in patients receiving computer-controlled propofol and manually controlled remifentanil infusions for minor surgery', *British. Journalof Anaesthesia*, vol. 90, no. 6, pp. 737-41.

Absalom, AR, Sutcliffe, N & Kenny, GN 2002, 'Closed-loop control of anesthesia using bispectral index: performance assessment in patients undergoing major orthopedic surgery under combined general and regional anesthesia', *Anesthesiology*, vol. 96, no. 1, pp. 67-73.

Alonso, H, Lemos, JM & Mendonca, T 2008, 'A target control infusion method for neuromuscular blockade based on hybrid parameter estimation', Proceeding of 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Vancouver, British Columbia, Canada, on August 20-24, 2008, pp. 707-710.

Asteroth, A, Moller, K & Schwilden, H, 1997, 'Adaptive control in anaesthesia', Proceedings of the IEEE Workshop on Neural Networks for Signal Processing, Amelia Island, Florida, on 24-26 Sep, 1997, pp. 236-243.

Bailey, JM & Shafer, SL 1991, 'A simple analytical solution to the three-compartment pharmacokinetic model suitable for computer-controlled infusion pumps', *Biomedical Engineering, IEEE Transactions on*, vol. 38, no. 6, pp. 522-5.

Bailey, JM & Haddad, WM 2005, 'Drug dosing control in clinical pharmacology', *Control Systems Magazine, IEEE*, vol. 25, no. 2, pp. 35-51.

Bamdadian, A, Towhidkhah, F & Moradi, MH 2008, 'Generalized predictive control of depth of anesthesia by using a pharmocokinetic-pharmacodynamic model of the patient', The proceeding of The 2nd International Conference on Bioinformatics and Biomedical Engineering, Shanghai, China, on 16-18 May, 2008, pp. 1276-1279.

Beneken, JEW & van Oostrom, JH 1998, 'Modeling in Anesthesia', *Journal of Clinical Monitoring and Computing*, vol. 14, no. 1, pp. 57-67.

Bequette, BW 2007, 'Non-linear model predictive control: a personal retrospective', *The Canadian Journal of Chemical Engineering*, vol. 85, no. 4, pp. 408-15.

Bibian, S 2006, 'Automation in clinical anesthesia', PhD thesis, University of British Columbia, 2006.

Bibian, S, Ries, CR, Huzmezan, M & Dumont, GA 2003, 'Clinical anesthesia and control engineering: terminology, concepts and issues', Proceedings of the European Control Conference, Cambridge, UK, on September 1‑4, 2003.

Bischoff, KB 1975, 'Some fundamental considerations of the applications of pharmacokinetics to cancer chemotherapy', *Cancer Chemotherapy Reports. Part 1*, vol. 59, no. 4, pp. 777-93.

Bouillon, T, Schmidt, C, Garstka, G, Heimbach, D, Stafforst, D, Schwilden, H & Hoeft, A 1999, 'Pharmacokinetic-pharmacodynamic modeling of the respiratory depressant effect of alfentanil', *Anesthesiology*, vol. 91, no. 1, pp. 144-55.

Bressan, N, Castro, A, Bras, S, Ribeirot, L, Ferreira, DA, Silva, A, Antunes, L & Nunes, CS 2007, 'Modelling the dynamics of depth of anaesthesia: Cerebral state index in dogs', The proceeding of the Control & Automation, Athens, Greece , on 27-29 July, 2007, pp. 1-5.

Brosilow, C & Joseph, B 2002, *Techniques of model-based control*, Prentice Hall PTR.

Brown, RH 1992, 'Risk and outcome in anesthesia', *Anesthesiology*, vol. 77, no. 4, p. 839.

Bruhn, J 1999, 'EEG indices and heart rate variability as measures of depth of anaesthesia', *British Journal of Anaesthesia*, vol. 83, no. 4, pp. 687.

Bruhn, J, Myles, PS, Sneyd, R & Struys, MMRF 2006, 'Depth of anaesthesia monitoring: what's available, what's validated and what's next?', *British Journal of Anaesthesia*, vol. 97, no. 1, pp. 85-94.

Caelen, O, Bontempi, G, Coussaert, E, Barvais, L & Clément, F 2006, ' Machine learning techniques to enable closed-loop control in anesthesia. ', Proceeding of the 19th IEEE International Symposium on Computer-Based Medical Systems, Salt Lake City, USA, on 05 June, 2006, pp. 696-701.

Cardoso, N & Lemos, JM 2008, 'Model predictive control of depth of anaesthesia: Guidelines for controller configuration', The Proceeding of the 30th IEEE Annual International Conference of the Engineering in Medicine and Biology Society, Vancouver, BC, 20-25 Aug. 2008, pp. 5822-5825.

Carson, ER & Jones, EA 1979, 'Use of kinetic analysis and mathematical modeling in the study of metabolic pathways in vivo', *New England Journal of Medicine*, vol. 300, no. 18, pp. 1016-27.

Chilcoat, RT 1980, 'A review of the control of depth of anaesthesia', *Transactions of the Institute of Measurement and Control*, vol. 2, no. 1, pp. 38-45.

Christofides, PD, Liu, J & Muñoz de la Peña, D 2011, 'Lyapunov-based model predictive control', in *Networked and Distributed Predictive Control*, Springer London, pp. 13-45.

Chuang, C-T, Fan, S-Z & Shieh, J-S 2009, 'Rule extraction by fuzzy modeling algorithm for fuzzy logic control of cisatracurium as a neuromuscular block', *Engineering Applications of Artificial Intelligence*, vol. 22, no. 1, pp. 129-40.

Copeland, SE, Ladd, LA, Gu, X-Q & Mather, LE 2008, 'The effects of general anesthesia on whole bBody and regional pharmacokinetics of local anesthetics at toxic doses', *Anesthesia & Analgesia*, vol. 106, no. 5, pp. 1440-9.

Dawes, J, Ng, L, Dorf, R & Cheung, T 1994, 'Design of deadbeat robust systems', Control Applications, Proceedings of the Third IEEE Conference on, 24-26 Aug 1994, pp. 1597-1598.

De Feo, O 2001, 'Modeling diversity by strange attractors with application to temporal pattern recognition', PhD thesis, Swiss Federal Institute of Technology Lausanne, Lausanne, Switzerland.

De Keyser, R & Ionescu, CM 2003, 'The disturbance model in model based predictive control', Control Applications, 2003. CCA 2003. Proceedings of 2003 IEEE Conference on, 23-25 June 2003.

Downey, D & Seagrave, RC 2000, 'Mathematical modeling of the human body during water replacement and dehydration: body water changes', *Annals of Biomedical Engineering*, vol. 28, no. 3, pp. 278-90.

Drummond, JC 2000, 'Monitoring depth of anesthesia: with emphasis on the application of the bispectral index and the middle latency auditory evoked response to the prevention of recall', *Anesthesiology*, vol. 93, no. 3, pp. 876-82.

Dumont, GA, Martinez, A & Ansermino, MJ 2009, 'Robust control of depth of anesthesia', *International Journal of Adaptive Control and Signal Processing*, vol. 23, no. 5, pp. 435-54.

Dutton, R, Smith, W & Smith, N 1995a, 'Wakeful response to command indicates memory potential during emergence from general anesthesia', *Journal of Clinical Monitoring and Computing*, vol. 11, no. 1, pp. 35-40.

Dutton, R, Smith, W & Smith, N 1995b, 'Brief wakeful response to command indicates wakefulness with suppression of memory formation during surgical anesthesia', *Journal of Clinical Monitoring and Computing*, vol. 11, no. 1, pp. 41-6.

Ejaz, K & Jiann-Shiou, Y 2004, 'Controlling depth of anesthesia using PID tuning: a comparative model-based study', Control Applications, 2004. Proceedings of the 2004 IEEE International Conference Taipei, Taiwan, on 2-4 Sept. 2004, pp. 580-585.

Ellis, KJ 2000, 'Human body composition: in vivo methods', *Physiological Reviews*, vol. 80, no. 2, pp. 649-80.

Emami-Naeini, A & Franklin, G 1982, 'Deadbeat control and tracking of discrete-time systems', *Automatic Control, IEEE Transactions on*, vol. 27, no. 1, pp. 176-81.

Engdahl, O, Abrahams, M, Bjornsson, A, Vegfors, M, Norlander, B, Ahlner, J & Eintrei, C 1998, 'Cerebrospinal fluid concentrations of propofol during anaesthesia in humans product information, diprivan(R), propofol', *British. Journalof Anaesthesia*, vol. 81, pp. 957 - 9.

Eshghi, N, Aliyari, M & Teshnehlab, M 2009, 'Anesthesia control based on intelligent controllers', Proceeding of the 3rd International Conference on Bioinformatics and Biomedical Engineering, Beijing, China, on 11-13 June 2009, pp. 1-4.

Foster, BL, Bojak, I & Liley, DTJ 2008, 'Population based models of cortical drug response: insights from anaesthesia', *Cognitive Neurodynamics*, vol. 2, no. 4, pp. 283-96.

Franklin, GF, Powell, JD & Emami-Naeini, A 1994, *Feedback control of dynamic systems*, vol. 2, Addison-Wesley Reading, MA.

Frei, CW, Gentilini, A, Derighetti, M, Glattfelder, AH, Morari, M, Schnider, TW & Zbinden, AM 1999, 'Automation in anesthesia', Proceedings of the American Control Conference, 2-4 Jun. 1999.

Furutani, E, Sawaguchi, Y, Shirakami, G, Araki, M & Fukuda, K 2005, 'A hypnosis control system using a model predictive controller with online identification of individual parameters', Control Applications, 2005. Proceedings of 2005 IEEE Conference, Toronto, Canada, on 28-31 Aug. 2005, pp. 154-159.

Furutani, E, Tsuruoka, K, Kusudo, S, Shirakami, G & Fukuda, K 2010, 'A hypnosis and analgesia control system using a model predictive controller in total intravenous anesthesia during day surgery', Proceedings of SICE Annual Conference, Taipei, Taiwan, on 18-21 Aug. 2010, pp. 223-226.

Gentilini, A, Schaniel, C, Morari, M, Bieniok, C, Wymann, R & Schnider, T 2002, 'A new paradigm for the closed-loop intraoperative administration of analgesics in humans', *Biomedical Engineering, IEEE Transactions on*, vol. 49, no. 4, pp. 289-99.

Gentilini, A, Rossoni-Gerosa, M, Frei, CW, Wymann, R, Morari, M, Zbinden, AM & Schnider, TW 2001, 'Modeling and closed-loop control of hypnosis by means of bispectral index (BIS) with isoflurane', *Biomedical Engineering, IEEE Transactions on*, vol. 48, no. 8, pp. 874-89.

Gentilini, A, Frei, CW, Glattfedler, AH, Morari, M, Sieber, TJ, Wymann, R, Schnider, TW & Zbinden, AM 2001, 'Multitasked closed-loop control in anesthesia', *Engineering in Medicine and Biology Magazine, IEEE*, vol. 20, no. 1, pp. 39-53.

Ghouri, AF, Monk, TG & White, PF 1993, 'Electroencephalogram spectral edge frequency, lower esophageal contractility, and autonomic responsiveness during general anesthesia', *Journal of Clinical Monitoring and Computing*, vol. 9, no. 3, pp. 176-85.

Glass, PS, Bloom, M, Kearse, L, Rosow, C, Sebel, P & Manberg, P 1997, 'Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers', *Anesthesiology*, vol. 86, no. 4, pp. 836-47.

Guedel, A 1920, 'Signs of inhalational anesthesia', *Inhalational Anesthesia. A Fundamental Guide.* New York: Macmillan, pp. 10-52.

Haddad, WM, Hayakawa, T & Bailey, JM 2006, 'Adaptive control for nonlinear compartmental dynamical systems with applications to clinical pharmacology', *Systems & Control Letters*, vol. 55, no. 1, pp. 62-70.

Heyse, B, VAN O, B, Wyler, B, Struys, M, Herregods, L & VEREECKE, H 2009, 'Comparison of contemporary EEG derived depth of anesthesia monitors with a 5 step validation process', *Acta Anaesthesiologica Belgica*, vol. 60, no. 1, p. 19.

Hoeven van der, S, Duncan, S, Farmery, A & Hahn, C 2007, 'Internal Model Control of inhaled anaesthesia', proceeding of American Control Conference, New York, USA, on 30 July 2007, pp. 582-587.

Homer, TD & Stanski, DR 1985, 'The effect of increasing age on thiopental disposition and anesthetic requirement', *Anesthesiology*, vol. 62, no. 6, pp. 714-24.

Hui-Hing, L, Beck, CL & Bloom, MJ 2004, 'On the use of multivariable piecewise-linear models for predicting human response to anesthesia', *Biomedical Engineering, IEEE Transactions on*, vol. 51, no. 11, pp. 1876-87.

Ionescu, CM, De Keyser, R & Struys, MMRF 2011, 'Evaluation of a propofol and remifentanil interaction model for predictive control of anesthesia induction', vol. 1, no. k21, p. k12.

Ionescu, CM, Hodrea, R & De Keyser, R 2011, 'Variable Time-Delay Estimation for Anesthesia Control During Intensive Care', *Biomedical Engineering, IEEE Transactions on*, vol. 58, no. 2, pp. 363-9.

Ionescu, CM, De Keyser, R, Torrico, BC, De Smet, T, Struys, MM & Normey-Rico, JE 2008, 'Robust predictive control strategy applied for propofol dosing using BIS as a Controlled Variable During Anesthesia', *Biomedical Engineering, IEEE Transactions on*, vol. 55, no. 9, pp. 2161-70.

Jacobs, JR 1988, 'Analytical solution to the three-compartment pharmacokinetic model', *Biomedical Engineering, IEEE Transactions on*, vol. 35, no. 9, pp. 763-5.

Janda, M, Simanski, O, Bajorat, J, Pohl, B, Noeldge-Schomburg, GFE & Hofmockel, R 2011, 'Clinical evaluation of a simultaneous closed-loop anaesthesia control system for depth of anaesthesia and neuromuscular blockade*', *Anaesthesia*, vol. 66, no. 12, pp. 1112-20.

Jensen, EW, Litvan, H, Revuelta, M, Rodriguez, BE, Caminal, P, Martinez, P, Vereecke, H & Struys, MMRF 2006, 'Cerebral state index during propofol anesthesia: a comparison with the bispectral index and the a-line ARX index', *Anesthesiology*, vol. 105, no. 1, pp. 28-36.

Jonker, DM, Visser, SAG, van der Graaf, PH, Voskuyl, RA & Danhof, M 2005, 'Towards a mechanism-based analysis of pharmacodynamic drug-drug interactions in vivo', *Pharmacology & Therapeutics*, vol. 106, no. 1, pp. 1-18.

Kaya, I 2004, 'IMC based automatic tuning method for PID controllers in a Smith predictor configuration', *Computers & Chemical Engineering*, vol. 28, no. 3, pp. 281-90.

Kennedy, JM & Van Riji, AM 1998, 'Effects of surgery on the pharmacokinetic parameters of drugs', *Clinical Pharmacokinetics*, vol. 35, no. 4, pp. 293-312.

Kenny, GNC & Mantzaridis, H 1999, 'Closed-loop control of propofol anaesthesia', *Br. J. Anaesth.*, vol. 83, no. 2, pp. 223-8.

Kissin, I 2000, 'Depth of anesthesia and bispectral index monitoring', *Anesthesia & Analgesia*, vol. 90, no. 5, pp. 1114-7.

Kreuer, S, Biedler, A, Larsen, R, Schoth, S, Altmann, S & Wilhelm, W 2001, 'The Narcotrend™– a new EEG monitor designed to measure the depth of anaesthesia A comparison with bispectral index monitoring during propofol-remifentanil-anaesthesia', *Der Anaesthesist*, vol. 50, no. 12, pp. 921-5.

Lee, JH, Morari, M & Garcia, CE 1994, 'State-space interpretation of model predictive control', *Automatica*, vol. 30, no. 4, pp. 707-17.

Lemos, JM, Roma, N, Mendonça, T, Sousa, L, Costa, B, Nunes, CS, Esteves, S, Amorim, P & Antunes, L 2006, 'Development of an integrated control system for anaesthesia automation', vol. 50, p. 1.

Linkens, DA & Mahfouf, M 2000, 'The Intelligent Systems in Biomedicine laboratory in the Department of Automatic Control and Systems Engineering at the University of Sheffield, UK', *Artificial Intelligence in Medicine*, vol. 21, no. 1-3, pp. 171-6.

Liu, N, Chazot, T, Hamada, S, Landais, A, Boichut, N, Dussaussoy, C, Trillat, B, Beydon, L, Samain, E, Sessler, DI & Fischler, M 2011, 'Closed-loop coadministration of propofol and remifentanil guided by bispectral index: a randomized multicenter study', *Anesthesia & Analgesia*, vol. 112, no. 3, pp. 546-57.

Lucchese, RR & McKoy, V 1983, 'Padé-approximant corrections to general variational expressions of scattering theory: application to 5σ photoionization of carbon monoxide', *Physical Review A*, vol. 28, no. 3, p. 1382.

Luginbühl, M, Bieniok, C, Leibundgut, D, Wymann, R, Gentilini, A & Schnider, TW 2006, 'Closed-loop control of mean arterial blood pressure during surgery with alfentanil: clinical evaluation of a novel model-based predictive controller', *Anesthesiology*, vol. 105, no. 3, pp. 462-70.

Mahfouf, M, Asbury, AJ & Linkens, DA 2003, 'Unconstrained and constrained generalised predictive control of depth of anaesthesia during surgery', *Control Engineering Practice*, vol. 11, no. 12, pp. 1501-15.

Mahfouf, M, Nunes, CS, Linkens, DA & Peacock, JE 2005, 'Modelling and multivariable control in anaesthesia using neural-fuzzy paradigms: part II. closed-loop control of simultaneous administration of propofol and remifentanil', *Artificial Intelligence in Medicine*, vol. 35, no. 3, pp. 207-13.

Malesani, L, Mattavelli, P & Buso, S 1998, 'Dead-beat current control for active filters', Industrial Electronics Society, 1998. IECON '98. Proceedings of the 24th Annual Conference of the IEEE, Aachen, on 31 Aug-4 Sep, 1998, pp. 1859 - 1864.

Malesani, L, Mattavelli, P & Buso, S 1999, 'Robust dead-beat current control for PWM rectifiers and active filters', *Industry Applications, IEEE Transactions on*, vol. 35, no. 3, pp. 613-20.

Manyam, SC, Gupta, DK, Johnson, KB, White, JL, Pace, NL, Westenskow, DR & Egan, TD 2006, 'Opioid-volatile anesthetic synergy: a response surface model with remifentanil and sevoflurane as prototypes', *Anesthesiology*, vol. 105, no. 2, pp. 267-78.

Marsh, B, Whitw, M, Morton, N & Kenny GNC 1991, 'Pharmacokinetic model driven Infusio of propolof in children', *British Journal of Anaesthesia*, vol. 67, no. 1, pp. 41-8.

Masui, K, Kira, M, Kazama, T, Hagihira, S, Mortier, EP & Struys, MMRF 2009, 'Early Phase Pharmacokinetics but Not Pharmacodynamics Are Influenced by Propofol Infusion Rate', *Anesthesiology*, vol. 111, no. 4, pp. 805-17 .

McAnulty, GR, Robertshaw, HJ & Hall, GM 2000, 'Anaesthetic management of patients with diabetes mellitus', *Br. J. Anaesth.*, vol. 85, no. 1, pp. 80-90.

Mendonca, T & Lago, P 1998, 'PID control strategies for the automatic control of neuromuscular blockade', *Control Engineering Practice*, vol. 6, pp. 1225-31.

Minto, C & Schnider, T 2008, 'Contributions of PK/PD modeling to intravenous anesthesia', *Clinical Pharmacology & Therapeutics*, vol. 84, no. 1, pp. 27-38.

Minto, CF & Schnider, TW 2008, 'Contributions of PK/PD modeling to intravenous anesthesia', *Clinical Pharmacology and Therapeutics*, vol. 84, no. 1, pp. 27-38.

Minto, CF, Schnider, TW & Shafer, SL 1997, 'Pharmacokinetics and pharmacodynamics of remifentanil: II. model application', *Anesthesiology*, vol. 86, no. 1, pp. 24-33.

Minto, CF, Schnider, TW, Egan, TD, Youngs, E, Lemmens, HJM, Gambus, PL, Billard, V, Hoke, JF, Moore, KHP, Hermann, DJ, Muir, KT, Mandema, JW & Shafer, SL 1997, 'Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil: I. model development', *Anesthesiology*, vol. 86, no. 1, pp. 10-23.

Mourisse, J, Lerou, J, Struys, M, Zwarts, M & Booij, L 2007, 'Multi-level approach to anaesthetic effects produced by sevoflurane or propofol in humans: 1. BIS and blink reflex', *British Journal of Anaesthesia*, vol. 98, no. 6, pp. 737-45.

Müller, T, Lauk, M, Reinhard, M, Hetzel, A, Lücking, CH & Timmer, J 2003, 'Estimation of delay times in biological systems', *Annals of Biomedical Engineering*, vol. 31, no. 11, pp. 1423-39.

Muñoz, HR, CortÃnez, LI, Ibacache, ME & Altermatt, FR 2004, 'Estimation of the plasma effect site equilibration rate constant (ke0) of propofol in children using the time to peak effect: comparison with adults', *Anesthesiology*, vol. 101, no. 6, pp. 1269-74.

Munson, ES & Bowers, DL 1967, 'Effects of hyperventilation on the rate of cerebral anesthetic equilibration: calculations using a mathematical model', *Anesthesiology*, vol. 28, no. 2, pp. 377-81.

Naguib, M, Magboul, A, Samarkandi, AH & Attia, M 1998, 'Adverse effects and drug interactions associated with local and regional anaesthesia', *Drug Safety*, vol. 18, no. 4, pp. 221-50.

Niño, J, Keyser, RD, Syafiie, S, Ionescu, C & Struys, M 2009, 'EPSAC-controlled anesthesia with online gain adaptation', *International Journal of Adaptive Control and Signal Processing*, vol. 23, no. 5, pp. 455-71.

Nunes, CS & Mendonça, TF 2005, 'Modelling propofol and remifentanil pharmacodynamic interaction using two different pharmacokinetic models: a comparative study'.

Nunes, CS, Mahfouf, M, Linkens, DA & Peacock, JE 2005, 'Modelling and multivariable control in anaesthesia using neural-fuzzy paradigms: part I. classification of depth of anaesthesia and development of a patient model', *Artificial Intelligence in Medicine*, vol. 35, no. 3, pp. 195-206.

Pilge, S, Zanner, R, Schneider, G, Blum, J, Kreuzer, M & Kochs, EF 2006, 'Time delay of index calculation: analysis of cerebral state, bispectral, and narcotrend nndices', *Anesthesiology*, vol. 104, no. 3, pp. 488-94.

Rao, RR, Aufderheide, B & Bequette, BW 1999, 'Multiple model predictive control of hemodynamic variables: an experimental study', Proceedings of the American Control Conference, San Diego, California, on 2-4 Jun 1999 , pp 1253-1257.

Rao, RR, Aufderheide, B & Bequette, BW 2003, 'Experimental studies on multiple-model predictive control for automated regulation of hemodynamic variables', *Biomedical Engineering, IEEE Transactions on*, vol. 50, no. 3, pp. 277-88.

Rezvanian, S, Towhidkhah, F, Ghahramani, N & Rezvanian, A 2011, 'Increasing robustness of the anesthesia process from difference patient's delay using a state-space model predictive controller', *Procedia Engineering*, vol. 15, pp. 928-32.

Robayo, F, Sendoya, D, Hodrea, R, Ionescu, C & de Keyser, R 2010, 'Estimating the time-delay for predictive control in general anesthesia', Proceedings of the Control and Decision Conference (CCDC), Xuzhou, China, on 26-28 May, 2010, pp 3719-3724.

Rosow, C & Manberg, PJ 2001, 'Bispectral index monitoring', *Anesthesiology Clinics of North America*, vol. 19, no. 4, pp. 947-66.

Sadean, MR & Glass, PS 2009, 'Pharmacokinetic-pharmacodynamic modeling in anesthesia, intensive care and pain medicine', *Current Opinion in Anesthesiology*, vol. 22, no. 4, pp. 463-8 10.

Saggini, S, Stefanutti, W, Tedeschi, E & Mattavelli, P 2007, 'Digital deadbeat control tuning for dc-dc converters using error correlation', *Power Electronics, IEEE Transactions on*, vol. 22, no. 4, pp. 1566-70.

Sakai, T, Matsuki, A, White, PF & Giesecke, AH 2000, 'Use of an EEG-bispectral closed-loop delivery system for administering propofol', *Acta Anaesthesiologica Scandinavica*, vol. 44, no. 8, pp. 1007-10.

Saldien, V, Vermeyen, KM & Wuyts, FL 2003, 'Target-controlled infusion of rocuronium in infants, children, and adults: A comparison of the pharmacokinetic and pharmacodynamic relationship', *Anesth Analg*, vol. 97, no. 1, pp. 44-9.

Sawaguchi, Y, Furutani, E, Shirakami, G, Araki, M & Fukuda, K 2008, 'A model-predictive hypnosis control system under total intravenous anesthesia', *Biomedical Engineering, IEEE Transactions on*, vol. 55, no. 3, pp. 874-87.

Schnider, TW, Minto, CF, Gambus, PL, Andresen, C, Goodale, DB, Shafer, SL & Youngs, EJ 1998, 'The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers', *Anesthesiology*, vol. 88, no. 5, pp. 1170-82.

Schnider, TW, Minto, CF, Shafer, SL, Gambus, PL, Andresen, C, Goodale, DB & Youngs, EJ 1999, 'The Influence of Age on Propofol Pharmacodynamics', *Anesthesiology*, vol. 90, no. 6, pp. 1502-16.

Schüttler, J & Ihmsen, H 2000, 'Population pharmacokinetics of propofol: a multicenter study', *Anesthesiology*, vol. 92, no. 3, pp. 727-38.

Schwilden, H & Olkkola, KT 1991, 'Use of a pharmacokinetic-dynamic model for the automatic feedback control of atracurium', *European Journal of Clinical Pharmacology*, vol. 40, no. 3, pp. 293-6.

Shafer, S, Longnecker, D, Tinker, J & Morgan, G 1998, 'Principles of pharmacokinetics and pharmacodynamics', *Principles and practice of anesthesiology. 2nd edn. DE Longnecker, JH Tinker, GE Morgan (eds). New York, Mosby-Year Book*, pp. 1159-210.

Shafer, SL & Gregg, KM 1992, 'Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer-controlled infusion pump', *Journal of Pharmacokinetics and Pharmacodynamics*, vol. 20, no. 2, pp. 147-69.

Sheiner, LB & Steimer, J-L 2000, 'Pharmacokinetic/pharmacodynamic modeling in drug development', *Annual Review of Pharmacology and Toxicology*, vol. 40, no. 1, pp. 67-95.

Shieh, J-S, Kao, M-H & Liu, C-C 2006, 'Genetic fuzzy modelling and control of bispectral index (BIS) for general intravenous anaesthesia', *Medical Engineering & Physics*, vol. 28, no. 2, pp. 134-48.

Shieh, JS, Linkens, DA & Asbury, AJ 2005, 'A hierarchical system of on-line advisory for monitoring and controlling the depth of anaesthesia using self-organizing fuzzy logic', *Engineering Applications of Artificial Intelligence*, vol. 18, no. 3, pp. 307-16.

Shridhar, R & Cooper, DJ 1997, 'A tuning strategy for unconstrained SISO model predictive control', *Industrial & Engineering Chemistry Research*, vol. 36, no. 3, pp. 729-46.

Snow, J 1847, *On the inhalation of the vapour of ether in surgical operations: containing a description of the various stages of etherization, and a statement of the result of nearly eighty operations in which ether has been employed in St. George's and University college hospitals*, J. Churchill.

Spence, AA 1988, 'THE LESSONS OF CEPOD', *British Journal of Anaesthesia*, vol. 60, no. 7, pp. 753-4.

Sreenivas, Y, Lakshminarayanan, S & Rangaiah, G 2007, 'A model predictive control strategy for the regulation of hypnosis', in R Magjarevic & JH Nagel (eds), *World congress on medical physics and biomedical engineering 2006*, Springer Berlin Heidelberg, vol. 14, pp. 77-81.

Sreenivas, Y, Yeng, TW, Rangaiah, GP & Lakshminarayanan, S 2009, 'A comprehensive evaluation of PID, cascade, model-predictive, and RTDA controllers for regulation of hypnosis', *Industrial & Engineering Chemistry Research*, vol. 48, no. 12, pp. 5719-30.

Steil, GM & Rebrin, K 2005, 'Closed-loop insulin delivery – what lies between where we are and where we are going?', *Expert Opinion on Drug Delivery*, vol. 2, no. 2, pp. 353-62.

Struys, MMRF, De Smet, T, Greenwald, S, Absalom, AR, Bingé, S & Mortier, EP 2004, 'Performance evaluation of two published closed-loop control systems using bispectral index monitoring: a simulation Study', *Anesthesiology*, vol. 100, no. 3, pp. 640-7.

Struys, MMRF, Vereecke, H, Moerman, A, Jensen, EW, Verhaeghen, D, De Neve, N, Dumortier, FJE & Mortier, EP 2003, 'Ability of the bispectral index, autoregressive modelling with exogenous input-derived auditory evoked potentials, and predicted propofol concentrations to measure patient responsiveness during anesthesia with propofol and remifentanil', *Anesthesiology*, vol. 99, no. 4, pp. 802-12.

Tan, W, Marquez, HJ & Chen, T 2003, 'IMC design for unstable processes with time delays', *Journal of Process Control*, vol. 13, no. 3, pp. 203-13.

Van Poucke, GE, Bravo, LJB & Shafer, SL 2004, 'Target controlled infusions: targeting the effect site while limiting peak plasma concentration', *Biomedical Engineering, IEEE Transactions on*, vol. 51, no. 11, pp. 1869-75.

Vanluchene, ALG, Vereecke, H, Thas, O, Mortier, EP, Shafer, SL & Struys, MMRF 2004, 'Spectral entropy as an electroencephalographic measure of anesthetic drug effect: A comparison with bispectral index and processed midlatency auditory evoked response', *Anesthesiology*, vol. 101, no. 1, pp. 34-42.

Volyanskyy, K, Haddad, WM & Bailey, JM 2009, 'Adaptive disturbance rejection control for compartmental systems with application to intraoperative anesthesia influenced by hemorrhage and hemodilution effects', *International Journal of Adaptive Control and Signal Processing*, vol. 23, no. 1, pp. 1-29.

Voss, GI, Katona, PG & Chizeck, HJ 1987, 'Adaptive multivarable drug delivery: control of artenal pressure and cardiac output in anesthetized dogs', *Biomedical Engineering, IEEE Transactions on*, vol. BME-34, no. 8, pp. 617-23.

Weber, F, Bein, T, Hobbhahn, J & Taeger, K 2004, 'Evaluation of the alaris auditory evoked potential index as an indicator of anesthetic depth in preschool children during induction of anesthesia with sevoflurane and remifentanil', *Anesthesiology*, vol. 101, no. 2, pp. 294-8.

Wen, P & Lu, TW 2008, 'Decoupling control of a twin rotor mimo system using robust deadbeat control technique', *Control Theory & Applications, IET*, vol. 2, no. 11, pp. 999-1007.

Westenskow, DR 1997, 'Fundamentals of feedback control: PID, fuzzy logic, and neural networks', *Journal of Clinical Anesthesia*, vol. 9, no. 6, Supplement 1, pp. 33S-5S.

Wiklund, RA & Rosenbaum, SH 1997, 'Anesthesiology', *New England Journal of Medicine*, vol. 337, no. 16, pp. 1132-41.

Yelneedi, S, Lakshminarayanan, S & Rangaiah, GP 2009, 'A comparative study of three advanced controllers for the regulation of hypnosis', *Journal of Process Control*, vol. 19, no. 9, pp. 1458-69.

Yelneedi, S, Samavedham, L & Rangaiah, GP 2009, 'Advanced control strategies for the regulation of hypnosis with propofol', *Industrial & Engineering Chemistry Research*, vol. 48, no. 8, pp. 3880-97.

Yue, D & Han, Q-L 2005, 'Delayed feedback control of uncertain systems with time-varying input delay', *Automatica*, vol. 41, no. 2, pp. 233-40.

Zanner, R, Pilge, S, Kochs, EF, Kreuzer, M & Schneider, G 2009, 'Time delay of electroencephalogram index calculation: analysis of cerebral state, bispectral, and narcotrend indices using perioperatively recorded electroencephalographic signals', *British Journal of Anaesthesia*, vol. 103, no. 3, pp. 394-9.

Zhang, K, Kang, Y, Xiong, J & Chen, J 1999, 'Deadbeat control of PWM inverter with repetitive disturbance prediction', Proceeding of the Fourteenth Annual Conference on Applied Power Electronics and Exposition, Dallas, TX, USA, on 14-18 Mar. 1999, pp. 1026-1031.

Zikov, T, Bibian, S, Dumont, GA, Huzmezan, M & Ries, CR 2002, 'A wavelet based de-noising technique for ocular artifact correction of the electroencephalogram', Proceeding of the 24th Annual Conference and the Annual Fall Meeting of the Biomedical Engineering Society Engineering in Medicine and Biology, the Second Joint, Houston, TX, USA, on October 23-26, 2002, pp. 98-105.