UNIVERSITI PUTRA MALAYSIA

SENSITIVITY ANALYSIS AND MULTI-MODEL GENERALISED PREDICTIVE CONTROL OF UNCERTAIN INTRAVENOUS GENERAL ANAESTHESIA SYSTEM

CHANG JING JING

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By

CHANG JING JING

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

June 2016

DEDICATIONS

To my parents,
teachers
and all educators.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

SENSITIVITY ANALYSIS AND MULTI-MODEL GENERALISED PREDICTIVE CONTROL OF UNCERTAIN INTRAVENOUS GENERAL ANAESTHESIA SYSTEM

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CHANG JING JING

June 2016

Chair: S. Syafiie, PhD

Faculty: Engineering

Feedback control of anaesthesia may offer a number of benefits. However, the design of the feedback controller is complicated by the presence of uncertainty due to inter-individual variability. As such, systematic analysis on the inter-individual variability is important to create better understanding on the system. This thesis aims to analyse the uncertainty in the dose-effect relationship and develop suitable controller(s) for intravenous general anaesthesia under the presence of uncertainty. Throughout the research, the propofol infusion rate and Bispectral Index (BIS) were considered as the control input and controlled variable, respectively.

The dose-effect relationship in biological systems is best described by the pharmacokinetic pharmacodynamic (PKPD) model. Inter-individual variability may arise from PK, PD or both. To quantify the effect of parametric variability in the propofol PKPD model on BIS uncertainty, a Sobol' variance based global sensitivity analysis was performed. Nine input factors were evaluated: patient's age, body weight, height, four PK model parameters and two PD model parameters. Result indicates that variability of PK model has a much smaller effect on BIS values compared to PD model. Among the input factors, Ce_{50} was the most significant variable in the PKPD model.

Inter-patient variability may lead to system instability. Therefore, it is important to know the uncertainty bounds acceptable by a controller to maintain system stability. While the variability in the nonlinear PD is much higher than the linear PK, most of the stability analyses have only considered modelling error that exists linearly. By employing circle criterion approach, the sector of nonlinearity that guarantees absolute stability of a closed-loop anaesthesia system was identified. It was found that the robust stability bound of the

specified control system is sufficiently large against the possible variability of nonlinearity among patients.

The PK model is a positive system. Imposing states positiveness in a closed loop system allows one to greatly simplify the stability analysis. Consequently, the controller design can be treated as a positive stabilisation problem. By making use of the positive nature of PK model, an observer-based output feedback controller was designed using a linear programming (LP) approach for uncertain PK models. However, simulation results show that the response of this controller was slow; a long induction phase duration (ID) was observed.

Finally, a multi-model generalised predictive controller with switching (MMGPC) was proposed. The idea is that, upon linearisation, important parameters variability can be reduced to one single factor, the process gain. Therefore, inter-individual variability among patient can be tackled by switching within models with different gain. The performance of MMGPC was evaluated and compared with three other extensions of GPC: the GPC with T polynomial (GPCT), the independent model GPC (GPCI), and the adaptive GPC (AGPC). Among these four controllers, MMGPC is found to perform the best; it has the lowest mean values for integral absolute error (IAE), the percentage of time of BIS outside 10 units from set point ($T_{\pm 10}$) as well as input signal's total variation (TV).

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

ANALISIS SENSITIVITI DAN KAWALAN RAMALAN MODEL DENGAN MODEL BERGANDA UNTUK SISTEM ANESTETIK UMUM DI BAWAH KETIDAKPASTIAN

Oleh

CHANG JING JING

June 2016

Pengerusi: S. Syafiie, PhD

Fakulti: Kejuruteraan

Kawalan gelung tertutup untuk sistem anestetik boleh mendatangkan banyak manfaat. Namun, reka bentuk pengawal adalah susah disebabkan oleh kehadiran ketidakpastian yang berasal daripada variabiliti antara pesakit. Oleh itu, analisis yang sistematik adalah penting untuk memahami sistem tersebut secara mendalam. Tesis ini bertujuan untuk menganalisis ketidakpastian tersebut dan merekabentuk pengawal yang sesuai untuk anestetic umum intravenus di bawah kehadiran sistem ketidakpastian. Tesis ini telah mengandaikan kadar infusi propofol sebagai kawalan input manakala Bispectral Index (BIS) sebagai kawalan output.

Model farmakokinetik-farmakodinamik (PKPD) merupakan model yang digunakan secara meluas untuk menerangkan hubungan dos-kesan ubat dalam sistem biologi. Ketidakpastian antara pesakit boleh berasal daripada PK, PD atau kedua-duanya. Untuk menilai kepentingan faktor-faktor model PKPD propofol dalam menganggar nilai BIS, Sobol' varians analisis sensitiviti global telah dijalankan. Sembilan faktor kemasukan telah dinilai, iaitu: umur, berat badan, ketinggian, empat faktor daripada PK dan dua faktor daripada PD. Keputusan menunjukkan bahawa variabiliti dalam faktor-faktor PD adalah lebih penting berbanding dengan variabiliti faktor-faktor PK. C_{e50} merupakan faktor yang paling penting dalam model PKPD tersebut.

Variabiliti antara individu boleh menyebabkan ketidakstabilan sistem. Oleh itu, pengetahuan mengenai batas ketidakpastian yang boleh disokong oleh sesebuah kawalan adalah penting. Walaupun variabiliti ketaklelurusan adalah agak besar berbanding dengan variabiliti faktor-faktor linear, kebanyakan analisis kestabilan hanya mempertimbangkan ralat model yang linear. Dalam tesis ini, kriteria bulatan telah diggunakan untuk mengidentifikasi sektor ke-

taklelurusan yang menjamin kestabilan mutlak sistem. Bagi sesebuah sistem yang ditunjukkan, analisis ini telah mendapati bahawa kawalan tersebut boleh menjamin kestabilan mutlak untuk kesemua variabiliti ketaklelurusan antara individu.

Model PK merupakan sistem positif. Mengenakan kepositifan keadaan (state) dalam reka bentuk pengawal boleh mempermudahkan analisis kestabilan. Hasilnya, reka bentuk pengawal boleh diselesaikan sebagai soal kestabilan positif. Dengan mengambil kira sifat positif model PK, satu pengawal suapbalik keadaan tercerap telah direkabentuk dengan menggunakan pengaturcaraan lelurus (LP). Malangnya, keputusan simulasi menunjukkan bahawa pengawal ini mempunyai tindak balas kawalan yang perlahan: tempoh fasa induksi yang panjang telah didapati.

Akhirnya, satu strategi kawalan ramalan model dengan model berganda dan pensuisan (MMGPC) telah dicadangkan. Idea ini adalah berdasarkan fakta bahawa selepas pelelurusan model tak lelurus, kepelbagaian boleh ditafsirkan dalam satu faktor tunggal,iaitu parameter gandaan. Oleh itu, kepelbagaian boleh ditangani dengan memilih rujukan model yang sesuai daripada model-model yang mempunyai parameter gandaan yang berbeza. Pengawal tersebut telah dinilai dan dibandingkan dengan prestasi tiga pengawal ramalan model (GPC) yang lain, iaitu: kawalan ramalan model dengan polinomial T (GPCT), kawalan ramalan model dengan model bersendiri (IMGPC), kawalan ramalan model adaptif (AGPC) dan kawalan ramalan model dengan model berganda (MMGPC). Antara keempat-empat pengawal ini, keputusan simulasi mendapati MMGPC mempunyai tindak balas yang terbaik; ia mempunyai nilai yang terendah bagi kamilan ralat mutlak (IAE), peratusan masa BIS terkeluar 10 unit daripada rujukan keluaran ($T_{\pm 10}$) dan juga jumlah variasi isyarat kawalan (TV).

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I certify that a Thesis Examination Committee has met on 8 June 2016 to conduct the final examination of Chang Jing Jing on her thesis entitled "Sensitivity Analysis and Multi-Model Generalised Predictive Control of Uncertain Intravenous General Anaesthesia System" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

Members of the Thesis Examination Committee were as follows:

Thomas Choong Shean Yaw, PhD
Professor Ir.
Faculty of Engineering
Universiti Putra Malaysia
(Chairman)

Samsul Bahari bin Mohd Noor, PhD
Associate Professor
Faculty of Engineering
Universiti Putra Malaysia
(Internal Examiner)

Mohammad Hamiruce Marhaban, PhD
Professor
Faculty of Engineering
Universiti Putra Malaysia
(Internal Examiner)

Ezra Kwok, PhD
Professor
University of British Columbia
Canada
(External Examiner)

ZULKARNAIN ZAINAL, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 23 August 2016

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of **Doctor of Philosophy**.

The members of the Supervisory Committee were as follows:

Syafiie, PhD
Senior Lecturer
Faculty of Engineering
Universiti Putra Malaysia
(Chairman)

Raja Mohd Kamil bin Raja Ahmad, PhD
Senior Lecturer Ir.
Faculty of Engineering
Universiti Putra Malaysia
(Member)

Lim Thiam Aun, MD
Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

BUJANG KIM HUAT, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

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Signature: _____
Name of Chairman of Supervisory Committee: Syafiie

Signature: _____
Name of Member of Supervisory Committee: Raja Mohd Kamil bin Raja Ahmad

Signature: _____
Name of Member of Supervisory Committee: Lim Thiam Aun

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LIST OF ABBREVIATIONS

AEP	Auditory Evoked Potential
AGPC	Adaptive Generalised Predictive Controller
AMG	Acceleromyography
ANFIS	Adaptive Neuro Fuzzy Inference System
ANI	Analgesia Nociception Index
ANOVA	Analysis of Variance
BIS	Bispectral Index
CARIMA	Controller Auto-Regressive Moving Average
CI	Cortical Input
CO	Cardiac Output
CS	Cortical State
CUP	Canonical Univariate Parameter
CV	Coefficient of Variance
DCU	Day Care Unit
DMC	Dynamic Matrix Control
EEG	Electroencephalography
EHAC	Extended Horizon Adaptive Control
EMG	Electromyography
EPSAC	Extended Prediction Self-Adaptive Control
FP	Factors Prioritisation
GPC	Generalised Predictive Control
GPCI	Independent Model Generalised Predictive Controller
GPCT	Generalised Predictive Controller with $T(z^{-1})$ Polynomial
HBI	Heart Beat Interval
HDMR	High Dimensional Model Representation
HRV	Heart Rate Variability
IAE	Integrated Absolute Error
ID	Induction Phase Duration
IM	Independent Model
IMC	Internal model control
LBM	Lean Body Mass
LMI	Linear Matrix Inequality
LP	Linear Programming
LRPI	Long Range Predictive Identification
LTI	Linear Time-Invariant
MAC	Model Algorithm Control
MAP	Mean Arterial Pressure
MIMO	Multi-input Multi-output
MISO	Multi-input Single-output
MMG	Mechanomyography
MMGPC	Multi-model Generalised Predictive Controller
MPC	Model Predictive Control
MUSMAR	Multivariable Adaptive Regulator

NLMS	Normalised Least Mean Square
NSRI	Noxious Stimulation Response Index
OAT	One-at-a-time
OS	Percentage of Overshoot
PACU	Postanaesthesia Care Unit
PBPK	Physiologically based Pharmacokinetics
PCI	Pertubational Complexity Index
PD	Pharmacodynamic
PFC	Predictive Functional Control
PI	Proportional-Integral
PID	Proportional-Integral-Derivative
PK	Pharmacokinetic
PKPD	Pharmacokinetic-Pharmacodynamic
PNS	Peripheral Nerve Stimulator
PONV	Postoperative Nausea and Vomiting
PPG	Pulse plethysmograhic
PPGA	Photoplethysmographic Pulse Wave Amplitude
RAS	Reticular Activating System
RL	Reinforcement Learning
RLS	Recursive Least Square
SD	Standard Deviation
SEP	Somatosensory Evoked Potential
SISO	Single-input Single-output
SPI	Surgical Pleth Index
TCI	Target Controlled Infusion
TOF	Train-of-four
TV	Total Variation
WAV_{CNS}	Wavelet-based Anesthetic Value for Central Nervous System
WTCRC	Wavelet Transform Cardiorespiratory Coherence

LIST OF NOMENCLATURES

BIS_0	Baseline BIS in the absence of drug
BIS_{min}	Minimum value of BIS, which is measured at the maximal drug effect
BIS_{nadir}	Lowest point of BIS during the induction phase
BIS_{target}	Targeted BIS
C_1	Drug concentration in central compartment ($\mu g/ml$)
C_2	Drug concentration in rapid peripheral compartment ($\mu g/ml$)
C_3	Drug concentration in slow peripheral compartment ($\mu g/ml$)
C_e	Drug concentration in effect-site ($\mu g/ml$)
C_{e50}	Drug concentration in the effect-site that produces 50 (%) of the maximum effect
E	Effect
E_{max}	Maximum effect of drug
E_0	Baseline effect in the absence of drug
k_{e0}	Rate constant of drug elimination from effect compartment (min^{-1})
k_{ij}	Rate constant of drug from the ith compartment to jth compartment (min^{-1})
u	Drug infusion rate (ml/h)
V_1	Volume of central compartment (l)
V_2	Volume of rapid peripheral compartment (l)
V_3	Volume of slow peripheral compartment (l)
γ	Steepness of the concentration-effect curve

Chapter 2

α	Normalisation constant ($\alpha = 60$ min/h)
ρ	Drug concentration (For propofol, $\rho = 10$ mg/ml)

Chapter 3

S_i	First order sensitivity index for ith input
Var_i	Variance of conditional expectation, given the ith input

Chapter 4

$\phi(.)$	Nonlinear function

Chapter 5

K	State feedback gain
k_r	Integral gain
L	Observer gain

Chapter 6

d	Dead time

N	Prediction horizon
N_u	Control horizon
Δ	Differencing operator ($\Delta = 1 - z^{-1}$)
δ	Output weighting sequence
λ	Control weighting sequence

CHAPTER 1

INTRODUCTION

1.1 Background

Anaesthesia administration is an evolving practice. Modern general anaesthetic techniques were shaped by human-refined definition of anaesthesia effect. Over the past few decades, technological advancements have affected the way on how anaesthetics were administered. In particular, the development of depth-of-anaesthesia monitors has shed new light on automatic control of anaesthesia. Nonetheless, automatic control of anaesthesia is complicated by system uncertainty such as inter-individual variability, disturbance and noise. In the next sections, a general background on the definition of anaesthesia, current clinical practice of general anaesthesia, related technologies and system uncertainties are introduced.

1.1.1 Definition of anaesthesia

The term *anaesthesia* originated from the Greek word which means insensibility. It was first proposed to describe the drug-induced temporary and reversible state of "unawareness" to render surgery painless by Oliver Wendell Holmes in 1846 (Rushman et al., 1996). Later, a more practical definition of anaesthesia was proposed, which define the anaesthetic state as a collection of "component" changes in behaviour. In 1950, Rees and Gray (Rees and Gray, 1950) defined the anaesthetic state as a triad with three components – narcosis, relaxation, and analgesia, produced by specific drugs with selective actions. Woodbridge (1957) further expanded anaesthesia into four components: sensory block, motor block, blockade of reflexes, and mental block. He believed that the state of general anaesthesia comprises of a spectrum of effects (components of anaesthesia) with different underlying mechanisms for different drugs.

Nowadays, it is generally accepted that anaesthesia is defined as a drug-induced, reversible state, comprises of at least three components: *hypnosis*, *analgesia* and *muscle relaxation* (Damian and Herlich, 2015; Whelan and Davies, 1990). The definition of each of these components were given as follows:

- *Hypnosis* is the general term used to describe loss of consciousness. It is the essential component of general anaesthesia. The loss of consciousness is induced and maintained by the general anaesthetic, which acts on the reticular activating system (RAS), thalamus, and cortex in the

brain (Damian and Herlich, 2015).

- *Analgesia* has two related meanings – the suppression of pain and the suppression of physiological reflexes due to surgical stimulation. As pain is usually considered as a conscious experience (Bischoff et al., 2008), in the context of general anaesthesia, the term analgesia is sometimes replaced by *antinociception*, which means the suppression of responds to potentially damaging stimuli (Merskey and Bogduk, 1994). Analgesia/antinociception is administered through opioids which blunts the nociceptive impulses at the level of spinal cord (Damian and Herlich, 2015).

- *Relaxation* refers to the suppression of movement in response to noxious stimulation. Movement can sometimes be retained even during unconsciousness. While muscle relaxation may be of less importance for some surgery, it is necessary in certain types of surgery or anaesthetic procedures such as intraabdominal and endotracheal intubation (Whelan and Davies, 1990), where immobility is required.

Each of these components may have varying priority, depending on the type of surgery and clinical condition. General anaesthesia, as opposed to local or regional anaesthesia, requires all these three components to be achieved. In local or regional anaesthesia, the purpose is to achieve analgesia and muscle relaxation in a specific part of the body. Patient's unconsciousness is not necessary. However, in general anaesthesia, hypnosis is an important endpoint.

Modern general anaesthetic techniques typically involve the combined use of a hypnotic drug, an opioid and/or a muscle relaxant (Urban and Bleckwenn, 2002) to achieve a desirable anaesthetic level. During the anaesthetic state, the cardiovascular, respiratory, autonomic and thermoregulatory stability of the patient must be preserved (Brown et al., 2010).

1.1.2 Current clinical practice

There are three main phases of general anaesthesia: induction, maintenance and recovery. Surgical procedure takes place during the maintenance phase.

During the induction phase, patient will be attached to the necessary monitoring equipment and anaesthetic machine. Then, the anaesthetist will induce anaesthesia by administering an appropriate dose of the hypnotic drug. The dosage is judged by the anaesthetist after considering the patient's age, weight and any associated disease. Any additional ancillary procedures such as intubation and insertion of additional intravascular lines will also be done at this stage.

The maintenance phase begins after the patient has lost consciousness. The maintenance phase requires the anaesthetist to be constantly vigilant in order to ensure that anaesthesia is deep enough to prevent any risk of awareness. Drug dosage is adjusted based on the clinical signs such as dilated pupils, tears, sweating, tachycardia and hypertension, patient movement, and respiratory rate (Dob and Haire, 2012; Sinha and Koshy, 2007; Bruhn et al., 2006). At the same time, he/she must avoid overdosage of drug that may lead to health complications. In addition, the anaesthetist will try to keep the patient's general condition in balance, which includes fluid management, replacement of blood loss, cardiorespiratory support and maintenance of body temperature.

As the operation comes to an end, the anaesthetist will stop the administration of drugs. The patients will be admitted to the Post-Anaesthesia Care Unit (PACU) for recovery. The length of stay in the PACU will depends on many factors, which include the dosing history from maintenance and induction phase (Soltesz et al., 2013b). A short recovery phase is preferable.

It can be seen that, in the clinical practice, the anaesthetist's experience and skill play an important role at effective regulation of anaesthesia. This is because the achievement of adequate anaesthesia requires the anaesthetist to constantly judge the depth of anaesthesia based on a multitude of parameters, and regularly adjust the dose of anaesthetic. In fact, skilled anaesthetist has been recommended as the best way to reduce intraoperative awareness (Orser et al., 2008). The quality of drug administration received by the patient is therefore subject to inconsistency depending on the anaesthetist's experience.

1.1.3 Anaesthetic agents

Anaesthetic agents can be administered by either intravenous infusions or inhalation, depending on the basis of their physical state. Inhalation anaesthetic is brought into the body via the lungs as a vapour or gas given through a face mask or airway device. On the other hand, intravenous anaesthetic is introduced to the body by injection into the vein as a bolus or through an infusion pump.

Regulation of depth of anaesthesia is easier for inhaled anaesthetics than with intravenous anaesthetics. This is because real time measurement of the concentration of anaesthetic in the gas that enters and leaves the lung is possible. The end-tidal concentration (concentration in the last part of the breath), is approximately equal to the partial pressure of anaesthetic in arterial blood (Eger, 1998). On the other hand, for intravenous anaesthetics, all the states are not available for real time measurement. It is only possible to estimate the anaesthetic concentration in the plasma. As such, inhaled anaesthetics allow a more precise control of the anaesthetic state.

In comparison to inhalation anaesthetics, the use of intravenous anaesthesia

during maintenance of general anaesthesia has been shown to improve early postoperative patient well-being, reduces the risk of postoperative nausea and vomiting (PONV) (Hofer et al., 2003), and shorten the PACU and day care unit (DCU) discharge times (Visser et al., 2001). In addition, the administration of intravenous drugs does not require specialized equipment such as the laryngeal mask airway, anaesthetic vaporizer and anaesthetic gas scavenger system for the delivery of anaesthetic vapours or disposal of exhaled gases. The introduction of target controlled infusion (TCI) system has further revolutionised the administration of intravenous anaesthesia. Details on the TCI system will be discussed in Section 1.1.4.1.

Examples of intravenous general anaesthetic agents currently in use include the propofol, etomidate, ketamine and thiopental. Among the various intravenous anaesthetic agents, propofol has been a favourable choice due to its notable advantages (McNeir et al., 1988). First, propofol is a fast-acting drug; general anaesthesia induced and maintained with propofol has a rapid and predictable emergence. Secondly, it causes minimal postoperative complications. For example, propofol does not causes adrenocortical suppression and is not potentiated by ethanol, diazepam, amitriptyline or phenelzine.

1.1.4 Related technologies

With the advancement of technologies, the practice of anaesthesia administration is experiencing a gradual change. One of the most remarkable changes is the employment of TCI pump in regulating intravenous anaesthetic agent (Cavaliere et al., 2001). Besides that, many commercialized monitors have been introduced to quantify the depth of anaesthesia. In this section, several technologies related to intravenous general anaesthesia are introduced.

1.1.4.1 Target controlled infusion (TCI)

In intravenous anaesthesia, anaesthetics were delivered to the patient through an infusion pump. In the early days, the infusion pumps were designed to deliver drugs in an adjustable, fixed infusion rate or dose rate (Milne and Kenny, 1998). However, this proves to be difficult to maintain a desired anaesthetic state.

As an illustration, to maintain the desired drug concentration in the effect site (brain), when the effect-site concentration is low, a high infusion rate (or bolus) of drug is desired. When the effect-site concentration begins to saturate, there should be a decrease in the drug infusion rate. However, this infusion rate should be high enough to replace the drug removed by metabolism or distributed to other parts of body. Hence, manual adjustment of a reasonable infusion rate according to the need of the patient is very

challenging.

A TCI pump incorporates a pharmacokinetic (PK) model to calculate the required infusion rate to achieve a targeted plasma concentration or effect-site concentration. In other words, the pump attempts to maintain a targeted plasma concentration or effect-site concentration instead of maintaining a fixed infusion rate. The calculation of the required infusion rate is performed using a population PK model programmed in the infusion pump. The first commercial TCI system for propofol, the 'Diprifusor', was launched in 1996 (Gray and Kenny, 1998). Currently, several TCI systems using different PK models for different drugs are commercially available.

TCI greatly simplifies the administration of intravenous drugs and is now a part of the routine anaesthetic techniques for the practitioner (Schraag, 2001). However, the TCI system is a model-based open-loop feedforward control system (Dumont, 2014; Ting et al., 2004). The target concentration is only a predicted value. It is not possible to verify that the target is actually achieved. It may suffer from inaccuracy when there is a model mismatch between the population PK model and the patient's model.

1.1.4.2 Measuring depth of anaesthesia

Clinical signs alone is said to be not reliable for measuring anaesthetic adequacy as it is subjective, discontinuous (Jensen et al., 2004), and vary considerably depending on patient, disease, drug and surgical technique (Schneider and Sebel, 1997). Hence, effort has been made to develop monitors that continuously "measure" the depth of anaesthesia.

Early concept considered the anaesthesia state as an all-or-none property (Sergent and Dehaene, 2004). However, recent researches propose that loss of consciousness is a graded event (Mashour, 2004; Noirhomme and Laureys, 2014); the level of unconsciousness is proportional to the reduction of cortical activity. Such a change in concept made the quantification of anaesthesia possible and led to the development of monitors measuring "depth" of anaesthesia.

With the advancement of sensor and signal processing, tremendous progress has been made in quantifying depth of anaesthesia. Many monitors for depth of anaesthesia have been commercialized, including the BIS™, Narcotrend™, PSA 4000™, AEP-Monitor/2™, Entropy Module™, CSM™, IoC™, Physio Doloris™ and EMG monitors.

Measuring depth of hypnosis

Up to now, electroencephalography (EEG) is the most reliable measurement for long-term monitoring of depth of hypnosis. EEG is the electrical activity

in the cerebral cortex produced by summation of inhibitory and excitatory postsynaptic potentials.

General anaesthesia is associated with a decrease in the average EEG frequency and an increase in the average EEG amplitude. With most anaesthetics, a deep level of anaesthesia induces burst suppression and then suppression of the whole EEG. The raw data from the EEG can be processed by several methods such as spectral analysis, entropy and wavelet analysis to yield useful information on the depth of hypnosis.

One of the most studied and investigated commercialized monitor to quantify depth of hypnosis is the Bispectral Index™ (BIS). It was introduced by Aspect Medical systems in 1992 (Rampil, 1998). It is based on bispectral analysis, which is a signal processing technique that quantifies quadratic nonlinearities and deviations from normality. The BIS index is an empirically derived parameter resulting from the weighted sum of a composite of multiple subparameters including bispectral analysis, burst suppression and β-activation. This information was combined using multivariate statistical modelling to form a single dimensionless index ranging from 0 (isoelectric state) to 100 (fully awake). The recommended value of BIS during surgical anaesthesia is 40 to 60.

EEG slows down and becomes more regular with deeper levels of unconsciousness. Hence, regularity of EEG can be used to measure the depth of anaesthesia. One way of measuring the regularity is by entropy, which measures disorder in signal. M-Entropy™ index which was introduced in 2003 employed spectral entropy analysis to estimate depth of anaesthesia (Vakkuri et al., 2004).

Wavelet analysis was used to process the EEG signal in NeuroSENSE™. Developed since 2003, this monitor quantifies the cortical state of the patient using $\mathrm{WAV_{CNS}}$ (Wavelet-based Anesthetic Value for Central Nervous System), a value based on wavelet analysis of the normalized EEG signal in the gamma frequency band (Zikov et al., 2006).

Another different approach to measuring electrical brain activity is the evaluation of auditory evoked potentials (AEP). Compared to the raw EEG, AEP is less sensitive to artifacts but poor in signal-to-noise ratio. The monitor extracts auditory evoked potential waves from the EEG signal by an autoregressive model with an exogenous input (ARX) adaptive model.

Other recently developed indices or advanced EEG analysis that may contribute to the measurement of depth of hypnosis includes the Pertubational Complexity Index (PCI) (Casali et al., 2013), Granger causality (Friston et al., 2013; Nicolaou et al., 2012), symbolic transfer entropy (Ku et al., 2011), permutation entropy (Jordan et al., 2008) (Marchant et al., 2014), and the cortical state (CS) and cortical input (CI) indices (Liley et al., 2010).

Measuring depth of analgesia
Generally, there is no direct method to measure analgesia when the patient is unconscious. The widely accepted indirect measures of analgesia are the heart rate variability (HRV), mean arterial pressure (MAP) (Gentilini et al., 2002), pupillometry (Larson et al., 1997), pulse plethysmographic (PPG) waveform (Rantanen et al., 2006), skin conductance level (Storm et al., 2002), ocular microtremors (Kevin et al., 2002) and frontal electromygraphy.

Based on these different modalities, several analgesia indices have been developed to quantify the analgesic state (nociceptive - antinociceptive balance). For example, the surgical pleth index (SPI™) (Huiku et al., 2007) was developed based on the photoplethysmographic pulse wave amplitude (PPGA) and normalized heart beat interval (HBI); the Analgoscore™ (Hemmerling et al., 2007) was developed based on mean arterial pressure (MAP) and heart rate; the analgesia nociception index (ANI™) (Logier et al., 2010) monitor was based on heart rate variability. In addition, skin conductance variability was used by the Med-Storm™ monitor (Storm et al., 2005) to quantify analgesia. Respiratory and heart rates was in the wavelet transform cardiorespiratory coherence (WTCRC) algorithm (Brouse et al., 2013). Another index which does not involve physiological measurements is the Noxious Stimulation Response Index (NSRI) (Luginbühl et al., 2010).

Measuring muscle relaxation
All techniques for assessing neuromuscular blockade use a peripheral nerve stimulator (PNS) to stimulate a motor nerve electrically. The pattern of PNS stimulation can be single-twitch, train-of-four (TOF), double-burst stimulation or tetanic stimulation. Assessing muscle responses by visual or tactile methods from PNS stimulation is often difficult and inaccurate. A number of mechanical (mechanomyography (MMG) and acceleromyography (AMG)) and electrical (electromyography (EMG)) methods are available for detecting and measuring these evoked responses more accurately (Appadu and Vaidya, 2008). Because MMG is unapplicable in routine clinical practice, most researchers prefer to use EMG, which is less vulnerable to mechanical interferences. In contrast to MMG and EMG, AMG is more user-friendly and is widely accepted and used in research (Claudius and Viby-Mogensen, 2008).

1.1.5 System uncertainty

One major challenge of the close-loop control of drug delivery system is the presence of uncertainty. This uncertainty may arises from many sources such as patient variability, disturbance, noise, and artifacts.

Inter-individual variability among patient is a major source of uncertainty. This variability can occur as a result of patient physiology (e.g. age, weight

and disease), variations in the PK processes (e.g. rate of absorption, distribution, metabolism, and excretion), and/or differences in the PD model (e.g. sensitivity of receptor, upregulation and downregulation). Further explanation on PK and PD models will be given in Chapter 2.

One early approach to account for the variability is by constructing a population PK model. Through population studies, significant covariates are identified and subsequently incorporated into the model. For example, for propofol PK model, Schnider et al. (1998, 1999) have incorporated age, total weight, and height into the model. In Marsh model, compartment volumes and clearances are assumed to be weight proportional (Marsh et al., 1991). Other population PK models for propofol includes the Björnsson (Björnsson et al., 2010), Schüttler (Schüttler and Ihmsen, 2000), Kataria (paediatric) (Kataria et al., 1994) and Eleveld (Eleveld et al., 2014) models. Nonetheless, these models only provide an estimation of the resulting anaesthesia effect. Their model parameters are subject to variation, and there is a high possibility that some unmodeled dynamics exist.

Besides inter-individual variability, the presence of disturbance, noise and artifacts are inevitable in the operating theatre. For example, surgical stimulation and blood loss are unavoidable during surgical procedure. Moreover, all measurable outputs are based on physiological signals which are potentially corrupted by artifacts (Gentilini et al., 2001a). These artifacts may result from the noise in measurement signals, detection-location changing or disconnection of sensors from the patient.

An ideal controller should be robust against these system uncertainty. However, resolving conflict between achieving robustness against uncertainty and maintaining a good control performance is a demanding problem (Hahn et al., 2011). Since patient's safety is the utmost important issue, the performance specification is rather strict. For example, the recommended boundaries of the depth of anaesthesia should not be violates to prevent any risk of awareness during surgery or overdose of drug.

1.2 Motivation

Feedback control of anaesthesia may offer a number of benefits to manual drug administration (Schwilden and Stoeckel, 1995; Gentilini et al., 2001a). It may improve patient's safety by avoiding drug overdose and intraoperative awareness, and performs consistently. It also helps to relieve the anaesthetist from the need to make recurrent and minor adjustments of drug dosage, thereby enabling the anaesthetist to concentrate on other critical issues. Furthermore,

an optimised drug administration may lower the healthcare cost by reducing the usage of drugs and shorten the recovery time. Finally, if tuned properly, closed-loop controllers can overcome the inter- and intra-individual variability, and provides drug dosages tailored to the precise needs of patient.

Technological advancements are paving the way for feedback control of anaesthesia too. Over the past few decades, there has been a significant improvement in the two most important prerequisites in closed-loop control system – the infusion pump (actuator) and the increasingly reliable monitors (sensor). With these improved prerequisites, the design of a reliable feedback controller for anaesthesia system has become a continuing effort among the research communities.

One of the major challenge in designing the controllers for anaesthesia system is the presence of inter-patient variability (Bibian et al., 2004). Some patients have a higher tolerance to drug effects and require a higher dose of drug. Some patients, on the other hand, are very sensitive to drug effects and need a lower dose of drug. Besides that, patient's sensitivity towards drug is rarely known *a priori* before the surgery. Hence, designing a controller for anaesthesia system is not an easy task, especially when the safety of patient must not be compromised.

In order to tackle the problem due to variability, systematic analyses on inter-individual variability should be carried out. A better understanding of the system can then be used to guide the design and analysis of the controllers.

1.3 Problem statement

Inter-individual variability can be arises from PK, PD or both. Anaesthetist has long suspected that the variability in the PD model is higher than variability in the PK model (Mertens and Vuyk, 1998). However, very few studies on quantification the effect of these variabilities have been performed.

Sensitivity analysis is a technique that investigate how the variations of model inputs attribute to the uncertainty of its output. Being one of the popular intravenous general anaesthetic, propofol's PKPD model should be assessed comprehensively. Recently, a local direct sensitivity analysis of propofol PKPD model has been conducted by Silva et al. (2014a) to identify significant and insignificant parameters of the model. However, local sensitivity analysis is not suitable for nonlinear model because it only assesses the model in the immediate region around nominal parameter values (Saltelli et al., 2004). Moreover, it only consider changes to one parameter at a time. In order to better reflect the importance of each parameters, a global sensitivity analysis on propofol PKPD model should be conducted.

Stability is a primary issue in every control system. Unfortunately, inter-

patient variability may lead to instability of control system (Bibian et al., 2004); in a clinical trial performed by Absalom et al. (2002), the same PID controller has been reported to provide adequate anaesthesia to some patients but cause oscillation in others. While it is suggested that variability in the nonlinear PD is much higher than variability in the linear PK, most of the robust stability analysis have only consider modelling error that exist linearly (Caiado et al., 2013; Ralph et al., 2011; Haddad et al., 2011; Sawaguchi et al., 2008). As a result, the stability analyses are incomplete. Hence, there is a need to perform stability analysis of an anaesthesia control system by considering variations in the model nonlinearity.

Apart from analysing the system stability only after the controller was designed, robust stability issue can also be tackled during the controller design process. This can be achieved by taking into account the positive nature of the PK subsystem (Farina and Rinaldi, 2000). Consequently, the control problem can be treated as a positive stabilisation problem. Since in most of the biological modellings, plant variability remains bounded with *a priori* known bounds (Gouzé et al., 2000), the variability can be accounted for during controller design using a linear programming (LP) approach (Rami and Tadeo, 2007). Due to the fact that the states of the anaesthesia system cannot be measured on-line, an observer is also added (Rami et al., 2011). Nonetheless, this controller is only suitable when the variability of nonlinearity is small.

When the inter-patient variability is large, a multi-model generalised predictive control (GPC) may be a promising control strategy. GPC is a popular control strategy due to a number of reasons (Clarke et al., 1987b): it has an inherent integral action to eliminate offset, it is capable to deal with unstable system, it shows a certain degree of robustness, and it allows the incorporation of control constraints. Note that GPC employed a linear model for prediction. A reasonable model candidate would be a linearised PKPD model. It is worth mentioning that upon linearisation of PKPD model, most of the variabilities can be represented by a single factor – the process gain. In other words, the inter-individual variability can be tackled by utilising prediction models with different process gain. Compared to fix controller or adaptive predictive controller, a multi-model GPC with switching is expected to give a safer, robust and more reliable performance.

1.4 Objectives

This research work aims to analyse and control uncertain system in intravenous general anaesthesia. Two analyses were performed, namely the sensitivity analysis and absolute stability analysis. The sensitivity analysis was performed on an open-loop anaesthesia model while the absolute stability analysis was performed on a closed-loop system. In addition, two types of controllers were developed. They are the observer-based output feedback con-

troller and the generalised predictive controllers (GPCs). More specifically, the objectives of this work are:

1. To analyse model uncertainty in the propofol PKPD model using global sensitivity analysis.
2. To analyse absolute stability of uncertainty in nonlinearity in closed-loop anaesthesia system using circle criterion.
3. To design observer-based output feedback controller that regulates depth of hypnosis of uncertain system by imposing state positiveness through linear programming (LP).
4. To develop a multi-model generalised predictive controller (MMGPC) to tackle model uncertainty.
5. To evaluate and compare the performance of multiple GPCs.

The first objective is to analyse the uncertainty in propofol PKPD model using global sensitivity analysis. Nine input factors are evaluated to assess their influences of each input parameters on the output uncertainty. They are the patient's age, body weight, height, four PK model parameters and two PD model parameters.

The second objective is to analyse the absolute stability of a closed-loop anaesthesia system with uncertainty in the nonlinearity. Through the analysis, the sector of uncertainty in nonlinearity that guarantees absolute stability of the system is identified.

The third objective makes use of the positive nature of PK subsystem to design an observer-based output feedback controller. With *a priori* known bound of parameter's variability, states positivity of the uncertain system can be imposed under state feedback controls using a LP approach. Since the states of anaesthesia system cannot be measured on-line, an observer is added to the control system.

Motivated by the effort to design a safe, reliable and robust controller, the fourth objective is to propose an MMGPC for the regulation of propofol infusion rate. The performance of this controller is then evaluated and compared with other extensions of GPCs. These controllers are tested for set-point changes, and disturbance, noise and time delay that may occur during the surgery.

1.5 Limitation and scope of study

In this thesis, all the analysis and controller designs have used propofol infusion rate as the model input and Bispectral Index (BIS) as the model output

(controlled variable). In other words, this work only concentrated on controlling hypnotic component of general anaesthesia. BIS was assumed as a reliable index that measures depth of hypnosis.

In Chapter 3, the relative importance of each model parameters is expressed in terms of their first order sensitivity index. Higher order sensitivity indexes are not computed because the purpose of this study is only on factor prioritisation.

Throughout the thesis, inter-individual variability only refers to parametric uncertainty. Uncertainty due to unmodeled dynamic was not considered.

Further, all control performances and studies presented in this thesis were only obtained through simulation. No clinical validation was performed.

1.6 Thesis layout

This thesis contains seven chapters addressing the descriptions, analyses and controls of uncertain system in intravenous general anaesthesia. The structure of the thesis is given below:

Chapter 1 provides the background of intravenous general anaesthesia and introduces the objective of the research. The background described includes the definition of anaesthesia, current clinical practice, anaesthetic agents, recent technologies in anaesthesia control, and uncertainty in anaesthesia system.

Chapter 2 presents an extensive review of the various modelling and control strategies applied in anaesthesia control system.

Chapter 3 quantifies the relative importance of input parameters of propofol PKPD model on BIS variability. The assessment is based on Sobol' variance sensitivity analysis.

Chapter 4 applies the circle criterion theorem to study the absolute stability of a given closed-loop anaesthesia system. The circle criterion systematically define the range of nonlinearity uncertainty that provides an absolute stable closed-loop system for a specified system.

Chapter 5 describes the control of hypnosis using an observer-based output feedback control. State feedback gain and observer gain were determined using a LP approach that ensure positiveness of states.

Chapter 6 proposes a new controller, MMGPC with switching, for the regulation of hypnosis using propofol. This chapter also evaluates and compares the performances of several extensions of GPC.

Finally, Chapter 7 concludes the thesis and provides recommendation for future work.

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