CLOSED-LOOP CONTROLLED TOTAL INTRAVENOUS ANAESTHESIA

by

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Anaesthesia is important for both surgery and intensive care and intravenous anaesthetics are widely used to provide rapid onset, stable maintenance, and rapid recovery compared with inhaled anaesthetics. The aim of the project on which this thesis is based was to investigate a reliable and safe methodology for delivering total intravenous anaesthesia using closed-loop control technology and bispectral analysis of human electroencephalogram (EEG) waveform. In comparison with Target Controlled Infusion (TCI), drug effect is measured during drug infusion in closed loop anaesthesia (CLAN). This may provide superior safety, better patient care, and better quality of anaesthesia whilst relieving the clinician of the need to make recurrent and minor alterations to drug administration.

However, the development of a CLAN system has been hindered by the lack of a 'gold standard' for anaesthetic states and difficulties with patient variability in pharmacokinetic and pharmacodynamic modelling, and a new and generic mathematical model of a closed-loop anaesthesia system was developed for this investigation. By using this CLAN model, investigations on pharmacokinetic and pharmacodynamic variability existing in patients were carried out. A new control strategy that combines a Proportional, Integral, Derivative (PID) controller, bispectral analysis of EEG waveform and pharmacokinetic/ pharmacodynamic models was investigated.

Based on the mathematical model, a prototype CLAN system, the first CLAN system capable of delivering both hypnotics and analgesics simultaneously for total intravenous anaesthesia, was developed. A Bispectral Index (BIS), derived from power spectral and bispectral analysis on EEG waveform, is used to measure depth of anaesthesia. A supervision system with built-in digital signal processing techniques was developed to compensate the non-linear characteristics inherent in the system while providing a comprehensive protection mechanism for patient safety. The CLAN system was tested in 78125 virtual patients modelled using published data. Investigations on intravenous anaesthesia induction and maintenance with the CLAN system were carried out in various clinical settings on 21 healthy volunteers and 15 patients undergoing surgery. Anaesthesia targets were achieved quickly and well maintained in all volunteers/patients except for 2 patients with clinically satisfactory anaesthesia quality.

Author's Declaration

At no time during the registration for the degree of Doctor of Philosophy has the author been registered for any other University award.

This study was carried out in collaboration with Derriford Hospital. Relevant scientific and engineering seminars and conferences were regularly attended at which work was always presented; clinical experts in Plymouth were visited for consultation purposes, and four papers were published.

Publications:

Dong C, Kehoe J, Henry J, Ifeachor EC, Reeve CD and Sneyd JR. *Closed-Loop_Computer Controlled Sedation with Propofol*. British Journal of Anaesthesia, 1998, **81,** 631p.

Dong C, Kehoe J, Henry J, Ifeachor EC, Reeve CD and Sneyd JR. *Does Notrous Oxide Affect Closed-Loop Sedation With Propofol*. British Journal of Anaesthesia, 1999a, **83,** 516p.

Dong C, Wrigley.S, Ifeachor EC, Reeve CD and Sneyd JR. *Closed-Loop Sedation During Knee Surgery Under Epidural Anaesthesia*. British Journal of Anaesthesia, 1999b, **83,** 516p-517p.

Sneyd JR, Dong C, Reeve CD and Ifeachor EC. *Using simulations in the design of an anesthesia system*. Simulation & Gaming,2001. **32**(2):pp 205-214.

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Signed 

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Glossary of Terms

STANPUMP	-- A TCI shareware program with pump driver
SIMO	-- Single-Input Multiple-Output
CLAN	-- Closed-Loop Anaesthesia
CACI	-- Computer Assisted Continuous Infusion
TCI	-- Target Controlled Infusion
DOA	-- Depth of Anaesthesia
PID	-- Proportional, Integral, Derivative
EEG	-- Electroencephalogram
BIS	-- Bispectral Index
SEF	-- Spectral Edge Frequency
MF	-- Median Frequency
AEP	-- Auditory Evoked Potential
AER	-- Auditory Evoked Response
PK	-- Pharmacokinetic
PD	-- Pharmacodynamic
C_T	-- Target Concentration
Cp_T	-- Target Plasma Concentration
Ce_T	-- Target Effect Site Concentration
Cp_{CALC}	-- Calculated Plasma Concentration
Ce_{CALC}	-- Calculated Effect Site Concentration
N_b	-- Early cortical latency in EEG waveform after auditory stimulation

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1. Introduction

Depth of anaesthesia monitoring is an important part of patient care. Anaesthesia is used in many areas such as dental surgery, surgical operation with incision, and intensive care. One of the aims of anaesthesia is to allow the patients to feel no pain and get into an unconscious state without memory in surgical operations.

However, it is harmful or even dangerous to patients if an excessive amount of drug is given. In order to control intravenous drug delivery, the depth of anaesthesia needs to be assessed. One critical problem often faced by anaesthetists in clinical practice is how to assess accurately the depth of anaesthesia in patients during surgery, and another is how much drug should be infused to achieve the desired depth of anaesthesia. It is desirable that the depth of anaesthesia could be assessed together with drug administration automatically and interactively with little human intervention as can be seen in many industrial processes.

At present, many anaesthetists are still delivering anaesthetic drugs manually using clinical signs (such as sweating, pupil size, etc.) to assess depth of anaesthesia. A primary aim of this project is to investigate the technology that provides automated intravenous drug administration and depth of anaesthesia assessment.

1.1. Background of Intravenous Drug Administration

The development of technology for intravenous drug delivery has evolved from manual delivery, automated model driven target controlled infusion (TCI) that is also known as computer assisted continuous infusion (CACI) (Alvis et al., 1985; Jacobs, 1990, 1995; Bailey and Shafer, 1991; Shafer and Gregg, 1992; Jacobs and Williams, 1993; Gray and Kenny, 1998), to today's closed-loop anaesthesia (CLAN) (Schwilden, Schuttler and Stoeckel, 1987; Kenny et al., 1992; Linkens, Shieh and Peacock, 1996; Webb, Allen and Smith, 1996; Roy and Huang, 1997; Linkens, Abbod and Backory, 1997; Mortier et al., 1998; Epstein, 1998; Morley et al., 2000; Absalom, Sutcliffe and Kenny, 2002; Wang and Wang, 2002). Although manual control of drug delivery is still the main method used in clinical practice, automated TCI has become more popular, while the CLAN system, though potentially the ultimate goal of intravenous anaesthetic drug administration, is still in early stages of research and development.

In manual control of anaesthesia, the clinician delivers anaesthesia by choosing a standard dose or dosage scheme of an anaesthetic agent and guessing the degree to which a specific

patient is sensitive or tolerant using information gathered by pre-operative history examination and clinical experience. The dosage scheme is then adjusted by trial and error with the objective of optimizing anaesthesia and avoiding toxicity. An anaesthesia syringe pump is commonly used for the manual infusion scheme, and anaesthetists usually pre-program the pump by using pharmacokinetics (PK), which characterizes mathematically the drug absorption, distribution, metabolism, and excretion. Usually, a bolus dose and a fixed maintenance infusion rate would be calculated from the mathematical PK model before the infusion. The bolus dose is for anaesthesia induction so that the desired drug concentration is achieved, while the maintenance infusion rate is to compensate for drug clearance over time.

Following advances in computer technology and the improvement in pump accuracy, the concept of using pharmacokinetics in manual delivery of an intravenous drug was combined with computer control technology. This resulted in the development of automated CACI (Computer Assisted Continuous Infusion) now widely known as TCI (Target Control Infusion). Research on CACI or TCI intravenous drug delivery has been active since the early 1980's, and resulted in the commercial TCI device "Diprifusor" (Glen, 1998).

A TCI system is an open loop system with the drug infusion rate controlled by a mathematical pharmacokinetic model of the drug. With a typical TCI system, the clinician simply sets a target concentration (either in plasma or at effect site) corresponding to the desired depth of sedation/anaesthesia for a specific patient, then the anaesthetic drug is infused automatically through an anaesthesia pump. The drug infusion rate is given by the PK model based on the difference between the desired and estimated concentrations (Jacobs, 1990, 1995; Bailey and Shafer, 1991; Shafer and Gregg, 1992; Jacobs and Williams, 1993). Manual calculation of induction bolus and the maintenance infusion rate is not needed if a TCI device is used, and the intervention from clinicians on drug administration is only required if adjustment on depth of sedation/anaesthesia is required.

The use of a TCI system relieves the anaesthetist of frequently making alterations on infusion rate, and the anaesthesia maintained by a TCI system is more stable than that maintained manually and less overshoot or undershoot were observed (Russell et al., 1995; Russell, 1998), hence it improves the quality of anaesthesia. However, an open loop control system requires a mathematical model with sufficient precision in describing the dynamic characteristics of the patients, and the PK model used in current TCI systems is far from exact with median absolute performance error (MDAPE) or median performance error (MDPE) of around 26% or 24% (Vuyk et al., 1995a), respectively. Pharmacokinetic parameters vary from

patient to patient (inter-patient variability) or even within a single patient over time (intra-patient variability), and this variability is not fully modelled. This implies that there is no set of pharmacokinetic parameters that apply to all patients in a population. In fact, the pharmacokinetic parameters used in a TCI system are the average values in a population. The anaesthetist needs to set a lower (or higher) target concentration for a specific patient who is judged as more (or less) sensitive to the drug than the population average based on clinical experience. Without feedback of measurement on drug effect, a TCI system is unable to adjust automatically the target concentration due to patient variability and intervention from the anaesthetist is required to do it manually.

The idea to provide the TCI system with a measurement of drug effect so that the target concentration is adjusted automatically leads to the development of closed loop control of intravenous anaesthesia. In a closed loop anaesthesia (CLAN) system, drug effect or depth of anaesthesia (DOA) is measured in real time and is compared with the target DOA to get an error signal. Then the CLAN system generates a drug infusion rate according to the error.

A CLAN system is potentially superior to an open-loop TCI system in many aspects. For a TCI system, the performance depends on the precision of patient model, while that of a CLAN system largely depends on the precision of drug effect measurement. A TCI system controls the drug concentration and ignores the pharmacodynamic characteristics in patients while a CLAN system controls the drug effect or depth of anaesthesia. As TCI is an open loop control system, any perturbation will not be addressed automatically. When anaesthesia is insufficient due to surgical stimulation or any other reason a CLAN system will respond by infusing more drug, and on the other hand, if the depth of anaesthesia is deeper than desired it will stop drug infusion. By using a CLAN system, the effect from patient variability would be minimized, and a better quality of anaesthesia maintained. In comparison with the use of a TCI system, intervention from a clinician during the drug infusion controlled by a CLAN system could be further reduced.

Closed loop control, also known as feedback control, is widely used in industry because of its superior control quality regardless of the type of object under control, in linear or nonlinear, time invariant or time varying. Even in the area of intravenous drug administration, closed loop control has been successful for regulating, for example, sodium nitroprusside(Behbehani and Cross, 1991) and muscle relaxant (Linkens and Hasnain, 1991) etc. In anaesthesia, although closed loop control systems delivering inhalational anaesthetic agents have already been built (Vishnoi and Roy, 1991; Jee and Roy, 1992), the development of closed loop

control system for intravenous anaesthesia has been slow and cautious due to various problems.

1.2. *Problems in Depth of Anaesthesia Monitoring*

The most common problem, faced by both clinicians and researchers in the area of depth of anaesthesia monitoring, is the lack of a 'gold standard' to define the anaesthetic states. This is a fundamental problem bringing difficulties for depth of anaesthesia measurement. Other problems in depth of anaesthesia monitoring are described below.

- **Pharmacokinetic/dynamic modelling**. The modelling of dose-effect relationship is known as pharmacokinetic and pharmacodynamic modelling that characterizes the drug distribution process up to the site of drug action. However the modelling error is still a significant concern. Median absolute performance error (MDAPE) or median performance error (MDPE) of 26% or 24% were reported (Vuyk et al., 1995a) on a population of patients in a propofol infusion study (Gepts et al., 1987).

- **Drug effect assessment**. It is extremely difficult for clinicians to assess quantitatively the depth of anaesthesia during surgery due to the lack of technology supporting on-line and objective assessment. Measurement of drug concentration from blood samples is only available off-line. In clinical practice, clinical signs (blood pressure, heart rate, pupil size, sweat etc.) and experience are still widely used. EEG monitors that calculate various spectral variables such as median frequency and beta power from the EEG waveform are helpful. However these EEG derivatives are not linearly correlated with drug concentration, and as such are of limited use. Recently, an EEG monitor that calculates the Bispectral Index (BIS) from EEG has been commercially available. Though some clinical researchers reported that this drug effect index is linearly correlated with propofol drug concentration (Leslie et al., 1995; Doi and Gajraj, 1997), it has not received universal acceptance from anaesthetists, and the linear relationship between this index and drug concentration is only valid in a statistical sense.

- **Patient variability**. Patient variability is part of the modelling problem and is caused by the incomplete modelling of the drug distribution process. In terms of drug distribution, every patient is unique and therefore the pharmacokinetic model and pharmacodynamic model of any patient are different from those of others, this is known as inter-patient variability. On the other hand, the pharmacokinetic model and

pharmacodynamic model change over time in a single patient, which is the so-called intra-patient variability. Patient variability comes from the different characteristics in patients such as sex, age, weight, height, drug history, fitness, etc. (Maitre et al., 1987; Stanski and Maitre, 1990; Minto et al., 1997; Schnider et al., 1999). Some of these factors are already modelled in pharmacokinetics albeit with modelling errors, but most of them are still unknown.

- **Hysteresis**. Though the plasma drug concentration peaks shortly after drug has been infused, it takes time for the drug to arrive at the site of drug action or effect site, this time is known as drug effect peak time (Schnider et al., 1999). The peak time varies from patient to patient, and could be changed even in a single patient over time.

- **Drug interaction**. In clinical practice, more than one drug is usually used in combination with other drugs, and some drugs interact with each other. This has been seen in general anaesthesia using propofol and alfentanil (Plummer and Short, 1992; Stanski and Shafer, 1995; Vuyk et al., 1995b; Vuyk, 1997, 1998; Rosow, 1997), for instance. Drug interaction is still a research topic.

- **EEG data quality**. At present, electroencephalogram (EEG) waveform is the only drug effect measurement available for on-line assessment of depth of anaesthesia (DOA). However, the measurement error of the EEG waveform has added uncertainty to the EEG variables. Bad epochs and artefacts in the EEG waveform could cause data rejection in EEG variable calculation. The impedance maintained between the skin and the electrodes could cause poor quality of EEG waveform. Interference may be increased by body movement.

1.3. Current State of the Art

As the site of action of anaesthetics is the central nervous system, the EEG signal, which is a record of brain activity, is important for the determination of depth of anaesthesia, and has been used as the only source to evaluate analytically the DOA in real time. However, the EEG signal itself is difficult to understand or interpret, and vulnerable to noise. It is necessary for the EEG signal to be processed with signal processing techniques in order to get meaningful interpretation. Various EEG derivatives or variables, for example, median frequency, Bispectral Index and auditory evoked response, have been derived from an EEG signal in this way and serve as the measure of DOA in CLAN systems.

The research on closed loop anaesthesia or CLAN systems started in early 1950s when Bickford and colleagues introduced the "servo-anesthetizer" (Bickford, 1950, 1951; Bellville, 1957) which regulates ether using integrated and rectified amplitude of the EEG signal. The system was tested on several animal species and humans, and promising results were obtained. However, the servo-anesthetizer was not widely accepted for it was difficult to determine which EEG derivative could be used as the measure of the DOA. Schwilden, Schuttler and their colleagues started research on CLAN systems from late 1980's (Schwilden, Schuttler and Stoeckel, 1987; Schuttler et al., 1995; Albrecht et al., 1997), and developed a system using the EEG median frequency (MF) as the measure of DOA. In the latest version of the system, a two-compartment PK model was incorporated into the control system, and an adaptive controller used to update part of the PK model parameters according to the error between the measured MF and the target MF. The system has been tested on several anaesthetic drugs including propofol and satisfactory results were reported (Schwilden, Schuttler and Stoeckel, 1987; Schwilden, Stoeckel and Schuttler 1989; Schwilden and Stoeckel 1993; Schuttler et al., 1995).

In the 1990s, more research groups became active in the research of CLAN system. Kenny et al. (1992) developed an anaesthetic index called AEP (Auditory Evoked Potentials) index, formerly known as LAS (Level of Arousal Score). As a measure of DOA, the AEP index is derived from the analysis of auditory evoked potential (AEP) of a human EEG signal and served as the feedback signal of their CLAN system. Functionally, the CLAN system consists of a proportional-integral (PI) controller and a standard TCI system with three-compartment pharmacokinetic model. The PI controller regulates the target concentration of the TCI system that generates infusion rates for the pump to maintain the target concentration. The system was tested for propofol infusion with patients breathing spontaneously and with those who received paralysing drugs during surgery. Satisfactory anaesthesia was reported (Kenny et al., 1993).

Advanced signal processing technologies have been introduced into this area. Roy and Hwang (1997) and Linkens et al. (1997) and their colleagues applied a wavelet transformation on the EEG derived auditory evoked potentials for feature extraction, and the extracted features are then fed into an artificial neural network for depth of anaesthesia classification. A fuzzy logic controller was used in Linkens' system to regulate directly the infusion rate, while in Roy's system, the infusion pump is controlled by STANPUMP, a research TCI system, and the target concentration of STANPUMP was regulated by a fuzzy logic controller. Webb et al. (1996) have done similar work by directly applying a neural network techniques to AEP

latency to determine the DOA and using a fuzzy logic controller to regulate the infusion rate. Satisfactory system performance was achieved in animal tests with Roy's system. However, no clinical testing on humans has been reported for these systems.

Due to the importance of clinical signs in determining the depth of anaesthesia in clinical practice, Linkens et al. (1996) developed a fuzzy logic controlled CLAN system using clinical signs. The numeric clinical signs (i.e. systolic arterial pressure and heart rate) are used to assess the primary DOA, and the anaesthetist's observations of sweating, lacrimation and pupil response are used to assess the degree of lightness of anaesthesia. Also the bolus drug effects are analysed to provide the patient sensitivity to the drug. Then the drug infusion rate is regulated by a rule base and a self-organising fuzzy logic controller, which take the primary DOA, degree of lightness and patient sensitivity as the inputs. The system has been tested in clinical trials as an intelligent adviser.

The investigation of an adviser (Epstein, 1998) on DOA monitoring and maintenance by an expert system approach is also reported. The system incorporates the measurements of BIS, BIS variability, heart rate, blood pressure, end tidal anaesthetic gas concentrations, predicted effect site drug concentrations, and anticipated events.

More recently, bispectral analysis, another advanced signal processing technique that identifies the inter-frequency relationship of an arbitrary waveform, was introduced to the analysis of EEG signals. Consequently, by combining the results from bispectral analysis and traditional power spectral analysis of the EEG signal, a more reliable index for depth of anaesthesia, Bispectral Index (BIS), was commercially developed and evaluated (Billard et al., 1994; Leslie et al., 1995; Pearson et al., 1996; Liu, Singh and White, 1996; Sebel and Lowdon, 1997). Using the Bispectral Index as the measure of DOA and the feedback signal of the closed loop system, Morley and colleagues (Morley et al., 2000) designed and tested their simple PID (Proportional, Integral, Derivative) control system. The PID controller directly regulates the drug infusion rate according to the error, the integration error and the derivative error between the BIS target and the measured BIS, no pharmacokinetic/dynamic model was used in this system. Clinical experiments on patients (Morley et al., 2000) show that it was effective in maintaining a constant level of anaesthesia.

Mortier and colleagues developed their CLAN system using BIS (Mortier et al., 1998). An adaptive controller and a pharmacokinetic model are used in the system to adapt to the inter-patient variability, and the model parameters are updated according to the BIS measurement from the patient. Clinically satisfactory results have been obtained from their experiments on

patients (Mortier et al., 1998; Struys et al., 2001) with this system.

At the time of writing in 2003, two other CLAN systems were reported. Wang and Wang (2002) developed a system using BIS feedback plus a predictive control technique, while Kenny's group (Absalom, Sutcliffe and Kenny, 2002) employed a PID controller and a commercial TCI device, Diprifusor, in their CLAN system. In Wang's system, the drug infusion rate is controlled directly by a proportional (P) controller with compensation from a predictive controller that anticipates in advance the major surgical stimulations such as incision and closing. This control strategy resulted in a much better control performance than using a proportional controller alone. In Absalom's system, the drug infusion is controlled by a Diprifusor TCI device whose target plasma drug concentration is updated every 30 seconds by a PID controller based on the measured BIS and the BIS target. It was reported that clinically adequate level of anaesthesia was maintained in patients undergoing surgery by using this CLAN system.

1.4. Aims and Objectives of the Project

The aim of this project was to investigate closed-loop anaesthesia for total intravenous anaesthesia or general anaesthesia. As drug effect is measured during the drug infusion, closed loop control of anaesthesia and sedation may provide superior safety and better quality of anaesthesia while relieving the clinician of a need to make recurrent and minor alterations to drug administration. Potentially, closed loop controlled drug delivery could lead to better patient care by minimizing the possibility of excessive dosing and allowing prompt identification of and response to perturbations which might go unnoticed by a clinician or be deemed too small to merit manual alterations of drug administration. On the other hand, a CLAN system for total intravenous anaesthesia would provide an efficient way to deliver two drugs simultaneously and would also provide a valuable tool for clinical research, such as on drug interaction.

To achieve this aim, it requires the investigation of pharmacokinetic and pharmacodynamic variability in population patients, the development of the control system, and a number of clinical experiments on human volunteers and patients. The CLAN system would consist of a CLAN sub-system delivering intravenous hypnotic agent propofol, and a TCI sub-system delivering intravenous analgesic agent alfentanil.

The key objectives identified from this aim are to:

- develop a mathematical model for closed-loop anaesthesia system;
- investigate the pharmacokinetic and pharmacodynamic variability in patients;
- investigate the control strategy of drug administration;
- develop techniques to ensure patient safety in clinical experiments;
- develop signal-processing techniques to overcome the non-linear characteristics of the closed-loop system;
- develop a CLAN system with user interface delivering both hypnotics and analgesics simultaneously;
- develop techniques to online collect, store, and display clinical data and clinical events/comments;
- evaluate the CLAN system on human subjects.

1.5. Outline of the thesis

The thesis consists of eight chapters including an introduction to the research, medical and technological background, mathematical model development, investigation of key issues in closed-loop anaesthesia, and design and clinical evaluation of a prototype system.

Following the general introduction in this chapter, Chapter 2 gives the necessary background in intravenous anaesthesia. To help understand the choice of feedback signal for the closed-loop anaesthesia, various methods for depth of anaesthesia monitoring are introduced. Pharmacokinetics and pharmacodynamics, which are the theoretical basis for intravenous drug delivery, are summarised. Then the anaesthetic drugs, propofol and alfentanil that are chosen for evaluating the system are introduced. Also, the concepts of manual control, open loop control, and closed loop control of intravenous drug delivery are introduced and their advantages and disadvantages discussed. Finally, a brief introduction to the Aspect A-1000 EEG monitor and the Graseby 3400 anaesthesia pump are given.

Chapter 3 summarizes the principle of closed-loop control with special focus on PID control. It also introduces power spectral, bispectral analysis, and their application on EEG signal.

Chapter 4 gives details of the development of a generic mathematical model of closed-loop anaesthesia.

Chapter 5 presents the investigation of key issues of closed-loop anaesthesia, such as inter-patient variability and control strategy. The performance of the closed-loop anaesthesia control is also investigated. A journal paper was published on this work (Sneyd et al., 2001).

Chapter 6 presents the design of a CLAN system based upon the mathematical model. The CLAN system uses Bispectral Index, which is derived from the EEG signal measured by the Aspect EEG monitor, to measure and control the depth of anaesthesia. The CLAN system is capable of delivering total intravenous anaesthesia for the chosen drugs.

Chapter 7 describes the evaluation of the CLAN system on volunteers, and patients undergoing surgery. This work resulted in three publications (Dong et al., 1999a, 1999b, 1998).

Chapter 8 presents discussion and conclusion on this investigation and gives suggestions to future research.

2. Intravenous Anaesthesia

2.1. Introduction

The definition of depth of anaesthesia (DOA) is extremely varied, ranging from scientific discussions of the minimum alveolar concentration (MAC) for inhalational anaesthetics or plasma drug concentration for intravenous anaesthetics to clinical descriptions of "light", "moderate", or "deep" anaesthesia (Stanski, 1994). Currently, there is no accepted "gold standard" defining the state of anaesthesia. In fact, the definitions of anaesthesia depth have evolved with the drugs used in clinical practice. Consequently, the use of potent inhaled anaesthetics, opioids, and intravenous anaesthetics in modern clinical practice has precluded the unifying definitions of anaesthetic depth. Generally, there are at least four components to "anaesthetic depth": sedation/hypnosis, analgesia, amnesia, and blockade of reflexes, and different drugs could be used to achieve each effect. In intravenous anaesthesia, there are some ways available to assess the DOA among which are clinical signs based on the clinical observations, plasma drug concentration by assaying the blood samples taken from the patient, and EEG variables derived from the patient's EEG signal using signal processing techniques. The clinical signs and EEG derivatives can be observed or obtained in real time, whereas a significant delay is needed for the assaying of a blood sample and the assays are not generally available. In clinical practice, the assessment of DOA by clinical signs varies from anaesthetist to anaesthetist due to different experiences in anaesthetists. To achieve the desired anaesthetic depth, either inhaled anaesthetics or intravenous anaesthetics can be used. However, completely different methods are required to administer them. For intravenous drug delivery, manual delivery or automated target control infusion (TCI) is currently used in routine practice in operating theatre and intensive care unit (ICU). Pharmacokinetics and pharmacodynamics are essential concepts with which the intravenous drugs may be given to their best advantage. The use of pharmacokinetics and pharmacodynamics in the drug infusion using TCI technique leads to continuous infusion techniques. An anaesthesia pump is needed to drive the syringe in both methods. A variety of intravenous drugs are available to induce and maintain anaesthesia. Propofol is popular for sedation/hypnosis, and alfentanil is widely used for analgesia. The use of intravenous drugs provides a rapid onset and a quick recovery as well.

In the following sections, the basic background on depth of anaesthesia monitoring, intravenous drug delivery, and intravenous drugs to be used in this investigation is introduced.

2.2. *Monitoring Depth of Anaesthesia*

2.2.1. Clinical Signs

Clinical signs of anaesthetic depth include blood pressure (BP), heart rate (HR), HR variability, sweating, pupil size, lacrimation, (isolated arm and eye) movement and respiratory patterns etc. However, the use of muscle relaxants eliminates the rate and volume of respiration as the clinical signs of DOA (Stanski, 1994), it also makes interpretation of movement both difficult and imprecise in most clinical circumstances. Of the clinical signs blood pressure and heart rate are numerical signs, and all the others are not. In clinical practice, clinical signs are important for anaesthetists to assess the depth of anaesthesia and have been routinely monitored. However, it has not been possible to use clinical signs to generate uniform measures of depth of anaesthesia. The usefulness of the clinical signs may be changing over time, and the clinical signs may correlate with DOA for certain anaesthetics and may not for some others. Surgical stimulation may interfere with some of the clinical signs such as blood pressure, and many factors have influence on pulse rate.

2.2.2. Drug Concentration

Another way to assess depth of anaesthesia is to determine the anaesthetic drug concentration from assaying blood samples. After being administered intravenously, the drug is transferred with hysteresis to the rest of the body by blood circulation, and only part of the drug will reach its effect site or its site of action, i.e., the brain. The drug concentration in plasma peaks almost instantly then declines due to the elimination or distribution of the drug from the body or to the rest of the body, whereas the drug concentration at effect site increases gradually until the drug concentrations in plasma and at effect site equilibrate. The relationship between the dose of drug administered and the drug concentration in plasma is characterized by pharmacokinetics, while pharmacodynamics characterizes the relationship between the drug concentration in plasma and the drug concentration at effect site. However, the drug concentration at effect site is only a measure of pharmacological effect, and the depth of anaesthesia is a measure of drug effect. To estimate approximately the drug effect from the effect site drug concentration, a sigmoid model is available.

Ideally, the depth of anaesthesia could be estimated from the measure of drug concentration at effect site. However the effect site is not accessible, and instead, the plasma drug concentration is measured from blood samples. Pharmacokinetics and pharmacodynamics make the estimate of effect site concentration possible. As significant time is required in assaying a blood sample, the measurement of depth of anaesthesia from drug concentration is

usually reserved for clinical experiments where the drug concentrations are analysed and/or processed after the experiments.

2.2.3. Human Electroencephalogram (EEG) Signal

The human EEG signal represents the cortical electrical activity derived from summated excitatory and inhibitory postsynaptic activity, which are controlled and paced by subcortical thalamic nuclei. This electrical activity has direct physiologic correlates relevant to depth of anaesthesia. Cerebral blood flow and cerebral metabolism are related to the degree of EEG activity. The EEG is a valuable tool because it reflects cerebral physiology, and is a continuous and non-invasive measure, its pattern changes markedly on administration of anaesthetic drugs, and also it is not affected by neuromuscular blockers (Thornton and Newton, 1989). Figure 2-1 shows some sample EEG patterns at different stages of anaesthesia with different drugs. EEG generally changes from a low amplitude, high frequency signal while awake to a large amplitude, low frequency signal when deeply anaesthetised. These changes are traditionally described using the frequency bands shown in Table 2-1.

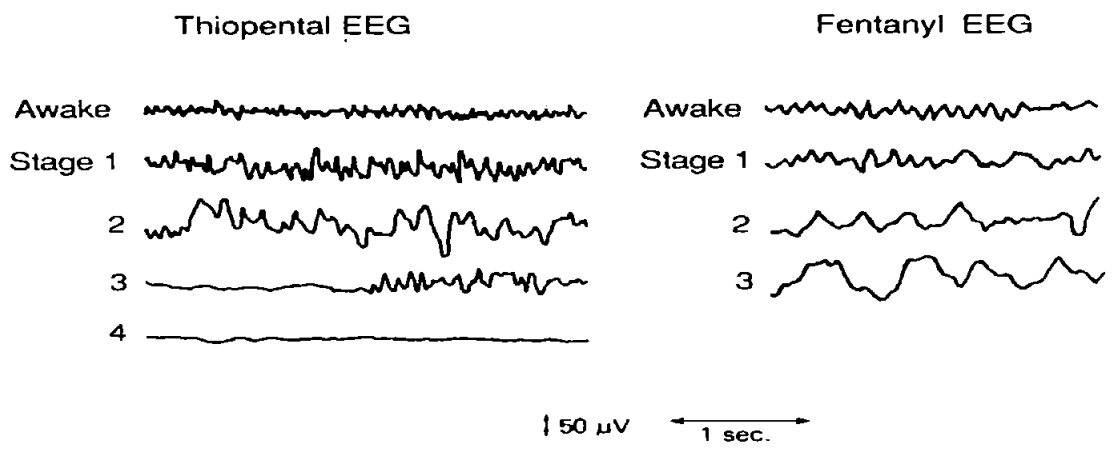


Figure 2-1 Increasing plasma concentrations of fentanyl or thiopental produce a characteristic progression of changes on EEG. In stage 1 (light anaesthesia), the frequency and amplitude of waveforms increase. In stage 2 (deeper anaesthesia), for both drugs produce a decrease in frequency and an increase in amplitude. In stage 3 (very deep anaesthesia), thiopental produces a burst-suppression pattern and finally, an isoelectric EEG.

Table 2-1 EEG frequency bands

EEG Frequency Band	Frequency Range (Hz)
Very low frequencies (Delta)	0-4
Low frequencies (Theta)	4-8
Medium frequencies (Alpha)	8-14
High frequencies (Beta)	14-30

The EEG signal has been used as an objective measurement of the depth of anaesthesia for a long time. However, the raw EEG signals, as seen in Figure 2-1, are difficult to understand, and different classes of anaesthetics are known to cause different EEG patterns. Some EEG patterns are generally associated with unconsciousness, and there is no EEG pattern that proves consciousness is present. In order to assess the depth of anaesthesia, meaningful features containing in a raw EEG signal and related to the depth of anaesthesia need to be extracted by means of signal processing.

Traditionally, the EEG signal is processed by Fourier transformation for power spectral analysis. Many variables were derived from the EEG by this method. For example, spectral edge frequency (SEF) and median frequency (MF) are defined as the frequencies below which 95% or 50% of the EEG signal power is located, respectively. Processed EEG variables from power spectral analysis are single-variable descriptors of depth of anaesthesia, and they are of limited use in describing depth of anaesthesia.

More recently, bispectral analysis was used to analyse the EEG signal, and a depth of anaesthesia indicator, Bispectral Index (BIS) (Billard et al., 1994; Leslie et al., 1995; Pearson et al., 1996; Sebel et al., 1997) was derived and made commercially available. BIS is a multi-variable depth of anaesthesia indicator that combines the results from bispectral analysis and those from power spectral analysis of the EEG signal. It was reported (Leslie et al., 1995; Doi et al., 1997) that BIS is linearly related to the propofol drug concentration over a clinically relevant range.

Another class of depth of anaesthesia descriptors is derived from the auditory evoked

response (AER), also known as the auditory evoked potential (AEP), produced by auditory stimulation of peripheral nerves. The AER is a subset of EEG signal and can be separated from the EEG signal by means of special signal averaging techniques. The AER can be divided into three responses: brain stem response obtained in the first 10ms after the stimulation, the early cortical response (15~80ms), and the late cortical response (80~100ms). Descriptors of depth of anaesthesia have been developed using AER (Kenny et al., 1992; Webb, Allen and Smith, 1996; Roy and Huang, 1997). A computer averaging technique, a neural network technique, and a wavelet transform were used for the developments.

2.2.4. Aspect A-1000 EEG Monitor

The Aspect Medical Systems A-1000 EEG Monitor is a patient-connected, user-configurable, four-channel EEG monitor, designed specifically for intra-operative or intensive care patient monitoring. An external analogue to digital signal converter (DSC), which can be placed close to the patient, is used to connect a patient to the monitor. With electrodes, the EEG signal of the patient can be measured with the DSC in either the bipolar or referential modes using up to four channels, then the DSC converts the analogue EEG signal into a digital signal and transmits it to the monitor. Subsequently, the digitised EEG signal is analysed within the monitor using power spectral and bispectral analysis techniques. A set of variables, including the Bispectral Index and median frequency, are derived from the signal processing. The update rate of the processed EEG variables is user selectable from 5, 10, and 30 to 60 seconds. A full list of the processed EEG variables and some relevant specifications are given in Appendix A. Either the raw EEG or the numerical value or trend of a processed EEG variable can be displayed on the monitor. Raw EEG data and the processed EEG parameters are also transmitted, in real time, to two RS-232 serial communication ports (i.e., raw EEG port and the processed EEG port), which makes it possible to record or process further the EEG data.

Bispectral Index is one of the key EEG variables provided by an Aspect EEG Monitor. Numerous versions of proprietary BIS algorithm have been commercially developed. BIS v3.12 was initially used in this project, and then it was updated to BIS v3.3. The latest version BIS XP has been optimised for intensive care.

2.3. Intravenous Drug Delivery

2.3.1. Pharmacokinetics

Pharmacokinetics characterises quantitative aspects of drug absorption, distribution,

metabolism and excretion, and describes the time course of drug and metabolite concentration at their "site of action". The mathematical model or physiological model (Glass et al., 1994) describing the distribution of drug in the body can be derived from experiments in which plasma drug concentration is measured at intervals after a bolus drug infusion, then non-linear regression is used to fit the concentration versus time curve. Linear approximation is applied during this modelling process, and the following poly-exponential expression, mathematically derived in Section 4.2, describes the drug distribution process in the body:

$$D_p(t) = \sum_{i=1}^{n} A_i e^{-\lambda_i t} \tag{2-1}$$

where $D_p(t)$ is the disposition function of the drug in the body after a bolus infusion, exponents λ_i are the inverse of the half-lives(half-life = $0.693/\lambda$), coefficients A_i are the relative contributions of each half-life to overall drug disposition, and the integer n is the number of exponentials (Glass et al., 1994). If the infusion rate over time is $I(t)$, then the plasma drug concentration over time, $Cp_{CALC}(t)$, is:

$$Cp_{CALC}(t) = I(t) * D_p(t) \tag{2-2}$$

where * denotes convolution. Examining the measured plasma concentrations over time (Glass et al., 1994), the plasma concentration peaks almost instantly after the bolus infusion of drug and then decays exponentially. In the development of the above pharmacokinetic model in Section 4.2, several assumptions have been implied. Basically, a PK model is assumed to be linear and stationary, i.e., giving a half or a double dose of drugs results in a half or a double set of concentrations and responses respectively, and the parameters in a PK model do not change over time. Another key assumption of a PK model is that it is valid for an individual patient as a representative of a population. The development of pharmacokinetic models provides a way to simulate the process of drug distribution in the body. Theoretically, the more exponential terms in $D_p(t)$, the higher precision the pharmacokinetic model provides. However in practice, usually two or three exponential terms in the pharmacokinetic model give reasonable results for most anaesthetic drugs (Glass et al., 1994), and it is unusual to use more than three exponential terms in practice for computational complexity would greatly increase. The following equation shows the tri-exponential drug disposition function:

$$D_p(t) = A_1 e^{-\alpha t} + A_2 e^{-\beta t} + A_3 e^{-\gamma t} \tag{2-3}$$

From the pharmacological point of view, when a certain dose of drug is given to a patient, the drug will be transferred from the plasma to the rest of the body including peripheral tissues,

organs, and fat stores, and part of the drug will be eliminated from the body. The drug transfer from the plasma to a certain part of the body stops when the drug concentrations at the two sites equilibrate. Following the further decline of the plasma concentration, redistribution of the drug from that part of the body to plasma would happen until the drug concentrations equilibrate again. This equilibration state is maintained dynamically between the plasma and the rest of the body. This drug disposition process is very much like a multi-compartment hydraulic model upon which the multi-compartment pharmacokinetic model was constructed. Figure 2-2 shows the generalized multi-compartment pharmacokinetic model while Figure 2-3 is a specific three-compartment hydraulic-like pharmacokinetic model.

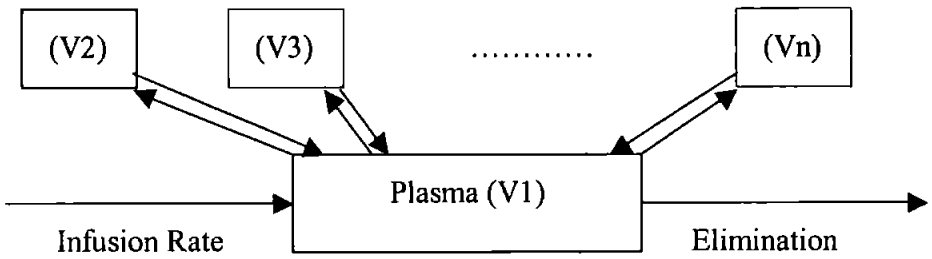


Figure 2-2 Generalized multi-compartment pharmacokinetic model of intravenous drug disposition (V*i* denotes the volume of the *i*th compartment)

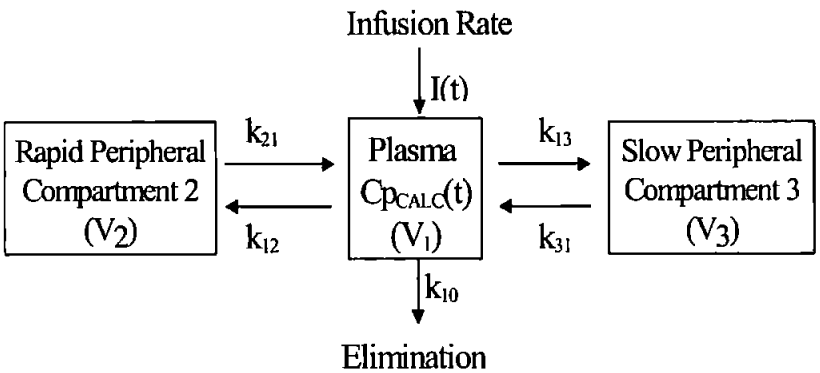


Figure 2-3 Three-compartment pharmacokinetic model of drug disposition following administration of intravenous drug. $Cp_{CALC}(t)$ (ng·ml^{-1}) is the drug concentration in central compartment. *V1*, *V2*, and *V3* (L) are the volumes of the three compartments, respectively. *I(t)* (μg·kg^{-1}·min^{-1}) is the drug infusion rate, k_{10} is the elimination rate at which drug is irreversibly removed from the plasma, and k_{12}, k_{21}, k_{13}, k_{31} are the inter-compartmental drug transfer rates.

In Figure 2-2, the central compartment or compartment 1 (V1) denotes the plasma, and the peripheral compartments represent different physiological parts of the body. The central plasma compartment includes "rapidly mixing portion of the blood and the first-pass of pulmonary uptake" (Glass et al., 1994), while the peripheral compartments "are composed of those tissues and organs showing a time course and extent of drug accumulation (or dissipation) different from that of the central plasma compartment" (Glass et al., 1994). Each physiological part is assumed to have the same drug transfer rates to and from the plasma. For example, a three-compartment pharmacokinetic model, shown in Figure 2-3, is composed of three physiological parts: plasma (compartment 1 or central compartment), a rapid equilibration part (compartment 2), and a slow equilibration part (compartment 3). The compartment 2 may roughly consist of muscle tissues, while the compartment 3 may correspond roughly to the fat stores. During the process of drug distribution and redistribution, part of the drug infused would be removed by the distributional clearance, metabolic clearance and terminal elimination.

The three-compartment hydraulic model shown in Figure 2-3 intuitively describes the process of drug disposition in the body, and it is easier to understand in comparison with its abstract mathematical description by equation (2-2) and (2-3). The parameters in both the mathematical model and the multi-compartment model can be mathematically transformed from one to another.

One of the important physiological parts in the human body is the effect site or the site of drug action. In definition, the effect site includes membranes, receptors, and enzymes, and more importantly the site is not accessible. According to clinical observations, additional time is needed for the drug concentration in the brain to rise and induce anaesthesia after a bolus infusion. This is so-called hysteresis of drug effect. The hysteresis varies from patient to patient and from one drug to another, and it may change intra-operatively within a single patient. Due to the transport clearance, the peak drug concentration at effect site or brain is lower than that in plasma. After a bolus dose, the drug concentration in plasma peaks almost instantaneously then declines, the effect site drug concentration rises slowly and peaks at the time when the drug concentrations in plasma and at effect site equilibrate. After the equilibration, both the plasma concentration and the effect site concentration decline. Although the effect site drug concentration is higher than that in plasma after the equilibration, the drug transfer from the plasma to the effect site is assumed irreversible. Part of the drug at effect site is also eliminated at a certain rate. This process can be described by adding the fourth compartment to the three-compartment model (Figure 2-4):

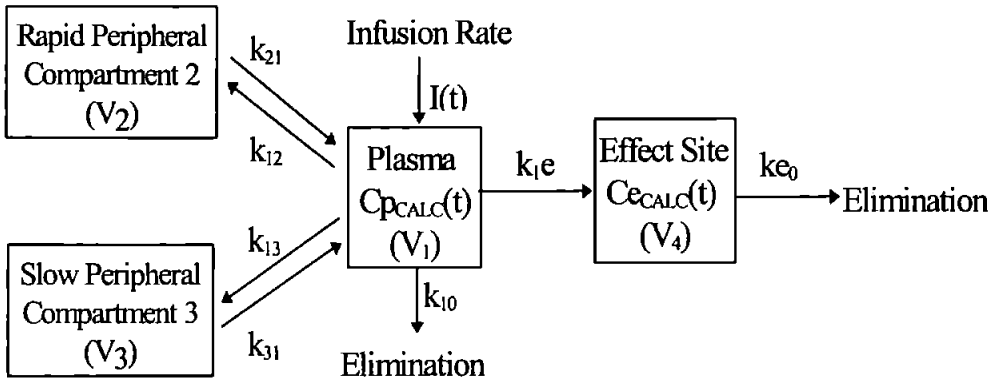


Figure 2-4 Three-compartment pharmacokinetic and one effect site compartment modelling for intravenous drug infusion

In Figure 2-4, k_{e0} is the elimination rate of the drug from the effect site to the environment, k_{1e} is the drug transfer rate from plasma to effect site, and the effect site volume (V_4) is negligible.

2.3.2. Pharmacodynamics

While pharmacokinetics describes the dose-concentration relationship, pharmacodynamics characterizes concentration-effect relationship. The concentration is the drug concentration at the site of action, i.e., the effect site drug concentration, and the effect could be any quantitative measurement of drug effect (or intensity of biological effect), including various EEG effects (e.g., Bispectral Index, median frequency or spectral edge frequency and so on). In pharmacology, a sigmoid model (Holford and Sheiner, 1981) shown in Figure 2-5 is used to show this concentration-effect relationship, and the mathematical expression of this relationship is presented in equation (2-4). In Figure 2-5, E is drug effect, C is effect site or steady-state plasma drug concentration, E_0 is baseline effect, E_{max} is maximum drug effect, C_0 is steady-state drug concentration when 50% of drug effect has been achieved, and γ is the steepness of the relationship curve. In Figure 2-5, zero concentration for zero effect is implied.

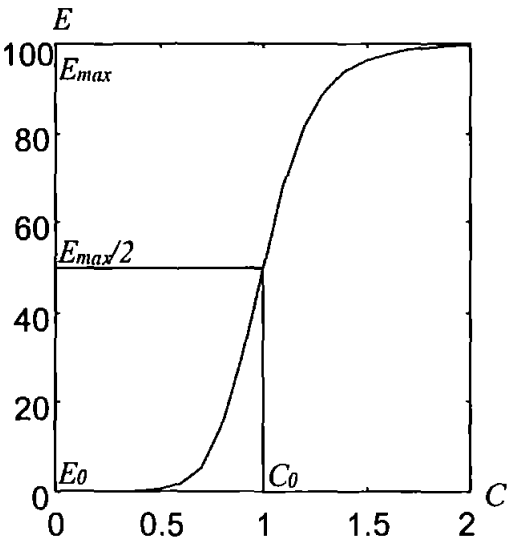


Figure 2-5 An example of sigmoid model of concentration-effect relationship (E denotes percentage of effect, C denotes steady-state drug concentration; E_{max}=100,E_0=0,γ=8,C_0=1)

$$E = E_{\max} \frac{C^{\gamma}}{C_0^{\gamma} + C^{\gamma}} - E_0 \qquad (2\text{-}4)$$

The sigmoid model is mathematically complex, especially when γ is not an integer, and the sigmoid model varies in patients with different parameters. In the example sigmoid model shown in Figure 2-5, the concentration-effect relationship could be considered as linear within a certain range of effect (10% - 80% in Figure 2-5). This property makes it possible for linear approximation of this model.

2.3.3. Accuracy of Pharmacokinetic Model and Patient Variability

At present, the accuracy of drug infusion by use of pharmacokinetic model is significant, the evaluation (Swinhoe et al., 1998) of the commercial Diprifusor TCI in patients undergoing major surgery shows that the performances of its drug concentration prediction are 16.2% of MDPE (Median Performance Error), and 24.1% of MDAPE (Median Absolute Performance Error). This evaluation also found that the measured propofol concentrations tended to be higher than the calculated concentrations using the PK model, especially after induction or an increase in target concentration.

Due to the physiological differences between patients, each of them has a unique pharmacokinetic/pharmacodynamic (PK/PD) model. That is, the parameters in the PK/PD model vary from patient to patient. Furthermore, the PK/PD parameters could change intra-

operatively during the process of drug delivery. The patient variability comes from both the pharmacokinetic side and the pharmacodynamic side. Usually pharmacodynamic variability exceeds pharmacokinetic variability, and inter-patient variability is large, whereas intra-individual differences are much smaller (Levy, 1998). Inter- and intra-variability in the patients cause the loss of accuracy (Ausems, Stanski and Hug, 1985; Maitre et al., 1988; Short et al., 1994; Vuyk et al., 1995a; Coetzee et al., 1995) of drug concentration estimation by a PK model. Currently, there is insufficient data on the degree of patient variability. The existence of patient variability therefore resulted in the development of population PK models (Maitre et al., 1987; Stanski and Maitre, 1990; Minto et al., 1997) and physiology based PK models (Wada and Ward, 1994, 1995; Cammarota and Onaral, 1998).

A population PK model would take into consideration the factors which alter the pharmacokinetics of a drug, such as height, weight, age, sex, disease state, induction agent, duration of anaesthesia, drug history (including the pre-medication) and so on. Although many pharmacokinetic models have been developed (Gepts et al., 1987; Cockshott et al., 1987; Shafer et al., 1988; Tackley et al., 1989; Marsh et al., 1991), they are all average population models. Stanski et al concluded that the pharmacokinetic mechanism for the decreased thiopental dose requirement in the elderly was a decreased rapid inter-compartment clearance, and there is no age-related change in brain responsiveness or pharmacodynamics when the spectral edge is used as a measure of drug effect (Stanski and Maitre, 1990). Egan et al. (1995) obtained the result that gender has no effect on the pharmacokinetics or pharmacodynamics of remifentanil. Minto et al (1997) reported that there is an effect of age on the pharmacokinetics and pharmacodynamics of remifentanil, and an effect of lean body mass on the pharmacokinetic parameters. However, there is no influence of gender on any pharmacokinetic or pharmacodynamic parameter. Schnider et al (1999) found that elderly patients are more sensitive to the hypnotic and EEG effects of propofol than are younger persons. In clinical practice, an average PK model, which is a representative of a population, is actually used.

In order to construct an average population model, three steps are required. Firstly, a mathematical model for each of the representatives of the population is built by experiment and non-linear regression on the experimental data. Those models are then mathematically transformed into compartment models, and finally the multiple sets of pharmacokinetic parameters in the compartment models are averaged to form a single set of parameters representing the average PK model. In practical use of the average pharmacokinetic model for drug infusion, the average physiological model needs to be transformed back into its

mathematical model in favour of computation.

2.3.4. Manually Controlled Drug Infusion

Manual delivery of anaesthetic drug is the traditional method to deliver anaesthesia using a high precision anaesthesia pump. It involves the calculation of a bolus dose which induces the anaesthesia and a maintenance infusion rate to maintain the anaesthesia.

As drug concentration is defined to be the amount of drug divided by volume (equation (2-5)), the induction bolus dose (B_d) can be therefore easily calculated from the target drug concentration (C_T) and the volume (V_1) of the patient as shown in equation (2-6).

$$Concentration = \frac{Amount}{Volume} \tag{2-5}$$

$$B_d = C_T \times V_1 \tag{2-6}$$

The bolus dose B_d calculated from equation (2-6) can be used to achieve the target drug concentration in plasma without overshoot. However most of the time in this case, the drug concentration in plasma is below the target. Alternatively, the central compartment volume V_1 in equation (2-6) can be replaced with the volume of distribution at the time of peak effect (V_4 in Figure 2-4), so that the drug concentration is equal to the target concentration when the plasma and the effect site are in equilibrium after the bolus infusion, although it results in overshoot in plasma.

After the bolus infusion, smaller infusion rates must be maintained to compensate the distribution loss and the clearance of drug. As the rate of distribution into peripheral tissues decreases over time, the maintenance infusion rate should therefore be changed accordingly. The following equation, derived from pharmacokinetic model, can be used for the calculation of maintenance infusion rate in a dosing regimen design.

$$Maintenance\ Infusion\ Rate = C_T \times V_1(k_{10} + k_{12}e^{-k_{21}t} + k_{13}e^{-k_{31}t}) \tag{2-7}$$

However few anaesthetists would mentally use this equation in their clinical practice. Average manual infusion dosing schemes, developed from PK/PD model, are available for various drugs. Table 2-2 shows the example schemes for the manual administration of propofol and alfentanil.

Table 2-2 Examples of manual infusion schemes when combined with 66% nitrous oxide and oxygen (Glass et al., 1994)

	Anaesthesia		Sedation or Analgesia	
	Loading Dose ug/kg	Maintenance Infusion ng/kg/min	Loading Dose ug/kg	Maintenance Infusion ng/kg/min
Propofol	1000 - 2000	80 - 150	250 – 1000	10 - 50
Alfentanil	50 - 150	0.5 - 3	10 - 25	0.25 – 1

2.3.5. Target Controlled Infusion

Target controlled infusion, also known as computer assisted continuous infusion (CACI), is an automated drug infusion method. The physical components in a TCI system include a high precision anaesthesia pump which drives a syringe, and a computer or microprocessor system controlling the infusion rate of the pump using a pharmacokinetic model. Currently, all TCI systems are for research except for the Diprifusor (Glen, 1998) which is commercially available.

From the point of view of a control strategy, target controlled infusion is an open loop control system (See Figure 2-6) for there is no measure of drug effect or patient response in the system. The system gives the drug according to the difference between the given target concentration (either in plasma or at effect site) and the drug concentration at the target site predicted by the built-in pharmacokinetic model. STANPUMP is one of such TCI systems.

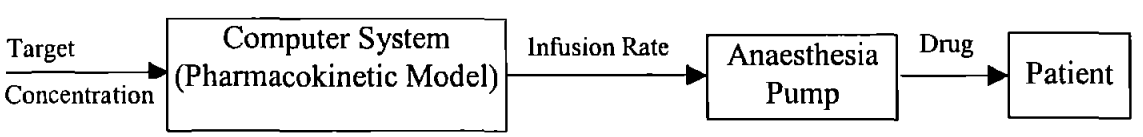


Figure 2-6 A Typical target controlled infusion system

Convenience, quick induction, less overshoot and less drug consumption are the main advantages of a TCI device over manual control (Russell, 1998), and 93% of the users prefer to use the TCI while 89% of the users found it easier to use in accordance with the report from Servin (1998).

2.3.6. Closed-loop Controlled Drug Infusion

The main drawback of a TCI system is the nature of open loop control strategy by which the system does not response to drug effect, patient response to the drug infused or depth of anaesthesia (DOA). A TCI system cannot automatically choose the pharmacokinetic model for a specific patient. In order to keep the anaesthesia at the same level, the anaesthetist needs to adjust manually the target concentration during maintenance in the light of clinical observations.

In the contrary, a closed loop anaesthesia (CLAN) system would give the drug to the patient according to the target drug effect and the real time measure of the drug effect from the patient. If any event happens and results in inadequate anaesthesia, a closed loop controlled anaesthesia system would respond to this event readily. Theoretically, a stable closed loop system has, inherently, the ability to minimise the error between the desired input and the measured output. This implies that a properly designed and implemented closed loop anaesthesia system is capable of inducing and maintaining the desired depth of anaesthesia in all patients in spite of the existence of patient variability and intra-operative surgical events causing inadequate anaesthesia.

Physically, a basic CLAN system would consist of a high precision anaesthesia pump including a syringe, an equipment measuring the DOA of the patient, a computer or microprocessor system incorporating a controller which controls the infusion rate of the anaesthesia pump by evaluating the measured DOA and the target. The block diagram of such a basic system is shown in Figure 2-7.

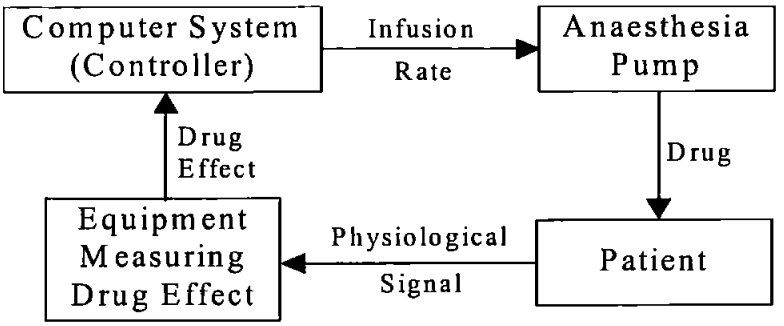


Figure 2-7 A basic closed loop anaesthesia system

Potentially, quality of anaesthesia control may be superior with a closed loop system. While inheriting the advantages from TCI, a CLAN system may provide more stable DOA and less overshoot. By reducing the requirement for clinician intervention to make frequent adjustments to anaesthesia, their time is spared to give better attention to other necessary tasks. One potential use of a CLAN system would be to allow a less skilled practitioner to deliver anaesthesia.

2.3.7. Graseby 3400 Anaesthesia Pump

Manufactured by Graseby Medical Limited, the Graseby 3400 anaesthesia pump is a clinical pump for administration of intravenous drugs by the way of driving a syringe which contains drug. When used for manual delivery of intravenous drug, a bolus dose can be specified in the pump for the induction, or one can set up a constant infusion rate for the maintenance of drug effect. The pump is capable of infusing intravenous drug at a rate from 0.1 ml/hour up to 1200 ml/hour. Alternatively, an external computer can be used to control remotely the pump through the RS232 serial communication port provided with the pump. Infusion rate, pump status, total infused volume and error messages can be controlled or inquired by the computer. However, the user can not press the "start" button on the pump to start the infusion when the pump is under the control of a computer.

2.4. Anaesthetic Drugs

2.4.1. Propofol

Propofol, also known as Diprivan (a trademark and the property of AstraZeneca PLC), is an intravenous anaesthetic agent. When infused into a patient, propofol forces the patient into the hypnotic state which is required for any surgery. Propofol was found to produce rapid onset of anaesthesia, short duration of action, satisfactory maintenance, and rapid recovery with

reliable amnestic properties (Sebel and Lowdon, 1989). Propofol can be used for sedation of patients in ICUs and has also been used for total intravenous anaesthesia combined with an opiate (e.g., alfentanil, fentanyl, or sufentanil etc.). In the elderly patient (Kirkpatrick et al., 1988), the clearance of propofol was significantly lower than in the younger patient. The volume of the central compartment in the elderly patient was also smaller than that in the younger patient. There were no differences in the volumes of distribution at steady state or in the half-lives of distribution and elimination. Less drug is therefore needed for the induction in elderly patients. The time for propofol to produce peak effect (i.e., peak time) after a bolus infusion was reported in the range of 1~2.4 minutes (Schnider et al., 1999). Many two- or three-compartment pharmacokinetic models have been developed with weight, age, sex, or height incorporated in some of these models. Table 2-3 shows a propofol pharmacokinetic model developed by Gepts and colleagues (Gepts et al., 1987).

The Gepts' rate constants were derived from a clinical study on 3 groups of 6 patients each undergoing surgery under regional anaesthesia. Propofol was infused in constant infusion rates of 3, 6, and 9mg/kg/hr respectively for at least 2 hours. Arterial blood samples were collected at selected times during and up to 8 hours after infusion.

The rate constants shown in the first column of Table 2-3 are the mean±standard deviation values among the 18 patients. The median absolute performance error (MDAPE) and the median performance error (MDPE) of this PK model are 26% and 24% (Vuyk et al., 1995a), respectively. The evaluation studies for computer controlled infusion of propofol on 5 (Vuyk et al., 1995a) and 3 (Coetzee et al., 1995) pharmacokinetic parameter sets show the pharmacokinetic parameters derived by Gepts et al (1987) are equally clinical acceptable with those derived by Cockshott et al (1987), Tackley et al (1989), Shafer et al (two-compartments) (1988), and Marsh et al (1991) while other two are less accurate.

Table 2-4 lists the good three-compartment pharmacokinetic parameter sets of propofol as the results of the comparison studies in (Vuyk et al., 1995a) and (Coetzee et al., 1995). In the meantime, the evaluation found that the plasma concentration was underestimated with all the good parameter sets, and a modified parameter set which is based on the parameters obtained by Gepts et al (1987) was recommended by Glass et al. (1989) and they are listed in the second column of Table 2-3. The recommended parameters are used in STANPUMP and also the CLAN system in this project.

Table 2-3 Pharmacokinetic parameters of propofol
from 18 subjects and the recommended modifications

PK Parameters	Mean ± SD Values Gepts et al. (1987)	Mean Values Glass et al. (1989)
K_{10} (min^{-1})	0.1190 ± 0.0351	0.152
K_{12} (min^{-1})	0.1140 ± 0.1051	0.207
K_{21} (min^{-1})	0.0550 ± 0.0558	0.04
K_{13} (min^{-1})	0.0419 ± 0.0155	0.092
K_{31} (min^{-1})	0.0033 ± 0.0013	0.0048
V_1 (L)	16.924 ± 6.9570	0.159w*

* w is the patient weight in kilogram

Table 2-4 Other popular pharmacokinetic parameter sets of propofol

PK Variables	**Marsh et al (1991)**	**Tackley et al (1989)**	**Cockshott et al (1987)**
k_{10} (min^{-1})	0.119	0.0827	0.1058
k_{12} (min^{-1})	0.112	0.105	0.1440
k_{13} (min^{-1})	0.0419	0.022	0.0282
k_{21} (min^{-1})	0.055	0.064	0.064
k_{31} (min^{-1})	0.0033	0.0034	0.0034
V_1 (L)	0.228w*	0.32w* or 22.4	17.5

* w is the patient weight in kilogram

2.4.2. Alfentanil

Alfentanil is an intravenous analgesic agent which relieves pain. It can be used either in surgery or in ICU. Alfentanil can be combined with a hypnotic for a total intravenous technique. Alfentanil has a short terminal elimination half-life (80-120 minutes) because of the relatively small steady-state distribution volume and a rapid plasma-effect site equilibration time (i.e., the drug effect peak time, 1~2 minutes) (Scott, Ponganis and Stanski, 1985) which results in a rapid onset of narcotic effect. Different surgical/anaesthesia stimuli require different alfentanil plasma or effect site concentrations to provide adequate clinical anaesthesia. However, if a hypnotic is used with alfentanil to induce anaesthesia, the dose of

the hypnotic can usually be markedly reduced. The infusion of alfentanil should be discontinued approximately 20 to 30 minutes prior to the expected end of surgery.

There are some pharmacokinetic models available for alfentanil. Shown in Table 2-5 is a typical population pharmacokinetic model developed by Maitre et al. (1987) based upon a clinical study on 45 patients. The PK model incorporates the sex, weight and age of individual patient, the mean bias (±SE) (systematic over- or under-prediction) of the model was –7.9±5.2%, and the mean absolute error (±SE) as a measure of the precision was 22.3±2.9% (Maitre et al., 1988).

Table 2-5 Pharmacokinetic parameters of alfentanil

PK Parameters		Value or Expressions
K_{10} (min^{-1})	Age > 40yr	$(0.356 - (0.00269 \cdot (Age - 40))) / V_1$
	Age≤40yr	$0.356/V_1$
K_{12} (min^{-1})		0.104
K_{21} (min^{-1})		0.0673
K_{13} (min^{-1})		0.017
K_{31} (min^{-1})	Age > 40yr	$0.0126 - (0.000113 \cdot (Age - 40))$
	Age≤40yr	0.0126
V_1 (litre)	Men	$0.111 \cdot$ Weight (in kg)
	Women	$0.111 \cdot 1.15 \cdot$ Weight (in kg)
t_p (min)		1.376

2.4.3. Drug Interaction between Propofol and Alfentanil

In clinical practice, inhalational or intravenous anaesthetic agents are combined to reduce the dose requirements of the individual agents, to diminish the incidence of side effects during induction and maintenance of anaesthesia, or to increase the speed of recovery. As propofol and alfentanil are both short action anaesthetic agents, they are frequently used in combination. However, there is drug interaction (Plummer and Short, 1992; Stanski and Shafer, 1995; Vuyk et al., 1995b; Vuyk, 1997, 1998; Rosow, 1997) for the combination use of analgesic and hypnotic agents, and/or the simultaneous use of several sedatives. Propofol will reduce the requirements of alfentanil concentration by interfering with its metabolism, and on the other hand alfentanil reduces the requirements of propofol concentration by reducing both the distribution and clearance of propofol (Vuyk et al., 1995b; Vuyk, 1998), which changes the dose-concentration-response relationship.

3. Closed-loop Anaesthesia

3.1. Introduction

Automatic control has played a very important role in the advance of engineering and science. It is extremely important to apply automatic control to auto-piloting systems such as in rockets (Choi, Bang and Kim, 1999), robots (Lacroix, Polotski and Cohen, 1999), and autonomous underwater vehicles (Craven et al, 1999). Since the advent of automatic control, it has become an important and integral part of modern manufacturing and industrial processes to improve productivity, replace routine repetitive manual operations, achieve and maintain the optimal performance of dynamic systems. Although its use in medical science is unusual, automatic control has been successfully used for the automated delivery of some types of drug, such as nitroprusside for blood pressure control (Behbehani and Cross, 1991), muscle relaxants (Linkens and Hasnain, 1991) and inhalational anaesthetics (Vishnoi and Roy, 1991).

All control systems could basically be classified into two categories: open loop control, and closed loop control that is also known as feedback control. While open loop control requires an accurate model for the controlled object or plant, the closed loop control needs to measure the plant output or states to adjust the input of the plant in order that the plant output approaches the desired or tracks the desired if it changes.

Digital signal processing has been widely used in modern control systems. In anaesthesia, power spectral analysis is a fundamental technique to process EEG signal and determine the state of anaesthesia. More recently, bispectral analysis, which reveals more hidden information carried in the EEG signal, has been used to produce the depth of anaesthesia descriptor Bispectral Index.

In this Chapter, the theoretical background on closed-loop control system with particular details on the proportional integral derivative (PID) controller is presented. The principle of higher order spectral analysis including power spectral and bispectral analysis is also introduced.

3.1.1. Open loop Control

Open-loop control systems are defined as those systems in which the output has no effect on the control action even if the output is measured or assessed in some way. One practical example of an open-loop control system is a washing machine that executes the scheduled events on a time basis according to how it is programmed. The accuracy of the open-loop

control depends on calibration or the mathematical model that describes the input-output relationship of the dynamic system. In any control system, an actuator that performs the control actions is needed and is either physically constrained or not. Where a constrained actuator is used, some open-loop control systems may be able to adjust the scheduled control signals to meet the requirements of the actuator. For example, a target controlled drug infusion system is a model-driven open-loop control system. The actuator of the system consists of a medical pump and a syringe which are physically constrained by the maximal pump speed, pump precision, syringe diameter and volume. One of the adjustments on the scheduled infusion rates in this open-loop control system is to clamp the infusion rate to the maximal infusion rate allowed when the scheduled infusion rate is higher than the maximal pump speed and also modify the following infusion rates to compensate the clamping.

Open-loop control systems will not perform the desired task if there is any disturbance or system non-linearity, or if there is any parameter that is time-varying or not modelled mathematically in the model that is used for the control. All these will affect the performance of open-loop control over the dynamic systems and cause an error between the system output and the command input (or desired system output). A strong motivation for using feedback signal in control systems is to reduce and correct this error. The use of feedback signal makes it possible for a control system to adapt those uncertainties.

3.1.2. Closed-Loop Control

Closed-loop control is also referred to as feedback control. In a closed-loop control system, the error signal that is the difference between the command input and the feedback signal is fed to the controller so as to adjust the control action that reduces the error. The feedback signal may be the output of the system or a function of the output signal and its derivatives, and affects system performance characteristics, such as stability, sensibility, and overall gain. The use of feedback makes the system response relatively insensitive to external disturbances and internal variations in system parameters, which is the main advantage over open-loop control. In order to obtain the same control accuracy, in open-loop control systems, accurate system models are required, while it is not necessary in closed-loop or feedback control systems because of this advantage. However, in some cases where the system dynamics are too complex or our knowledge of them is insufficient, the combination of open-loop control and closed-loop control is usually less expensive and will give satisfactory overall system performance. Figure 3-1 shows the block diagram of a closed-loop or feedback control system where the sensor provides he feedback signal by measuring the system response ($y(k)$) with

the presence of disturbance ($v(k)$), and the controller gives a control signal ($u(k)$) according to the error signal ($e(k)$) that is the difference between the command input ($x(k)$) and the feedback signal.

Consider a digital control system that has the block diagram shown in Figure 3-1. The pulse transfer function representation of the system is shown in Figure 3-2.

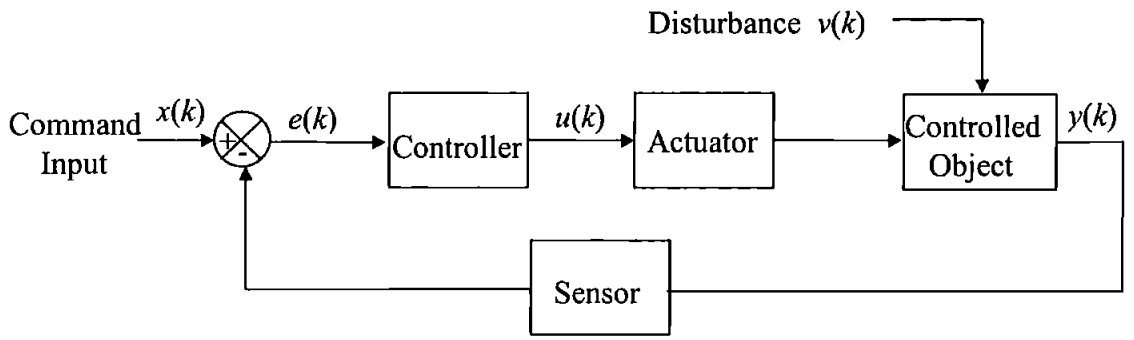


Figure 3-1 A typical closed-loop control system

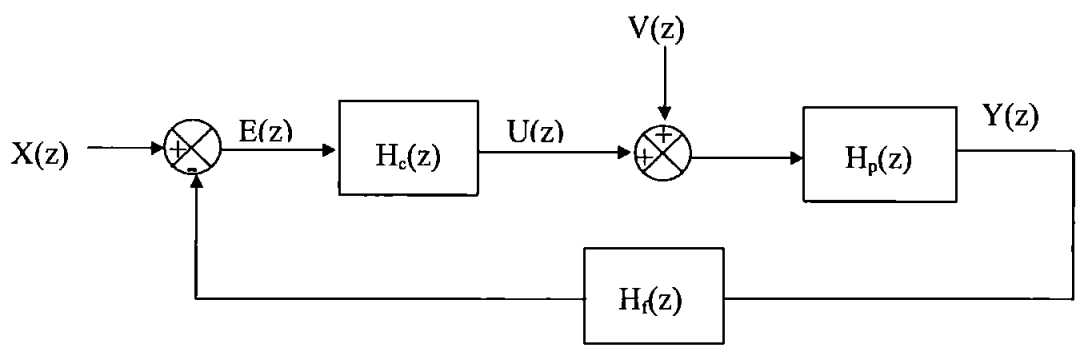


Figure 3-2 The pulse transfer function representation of the closed-loop control system

Where $H_c(z)$, $H_p(z)$, and $H_f(z)$ are the pulse transfer functions of the controller, plant (i.e. the controlled object), and the sensor in the closed-loop control system, respectively. $X(z)$, $E(z)$, $U(z)$, $V(z)$, and $Y(z)$ are the z-transform of the discrete command input, error signal, control signal, external disturbances, and the system output or response, respectively.

Suppose the disturbance of the control system is zero, then the open-loop pulse transfer function of the system in Figure 3-2 is defined as the product of all the pulse transfer functions in the closed feedback loop:

$$H(z) = H_c(z)H_p(z)H_f(z) \tag{3-1}$$

while the overall closed-loop pulse transfer function of the system is defined as:

$$G(z) = \frac{Y(z)}{X(z)} = \frac{H_c(z)H_p(z)}{1 + H_c(z)H_p(z)H_f(z)} = \frac{H_c(z)H_p(z)}{1 + H(z)} \tag{3-2}$$

The output and the error signal of the closed-loop control system are then

$$Y(z) = G(z)X(z) \tag{3-3}$$

$$E(z) = \frac{X(z)}{1 + H(z)} \tag{3-4}$$

3.2. *Closed-Loop Control Systems*

3.2.1. Introduction

For a given control problem, it is important to choose the appropriate control strategy and design the proper controller so as to achieve the desired performance of system control.

Various control strategies have been used in industry and many other areas including medicine, there is no such a control strategy that is the best for all control problems. The control strategies vary from conventional control (e.g., PID control), model reference control, optimal control, stochastic control, H_∞ control, to neural network control and fuzzy logic control. All control strategies could be full adaptive, part adaptive or non-adaptive. For some control strategies, one could be used in combination with another to form a new control scheme, for example, PID+reference model, PID+fuzzy, or neural-fuzzy.

Of all the control strategies, PID control might be the most successful control strategy used in control engineering in the past due to its simplicity and efficiency. It is especially useful if the plant dynamics are unknown or partly known. It is possible to obtain better performance of control from other control strategies, however the PID control usually gives satisfactory control.

There are many ways available for the design of a conventional single-input-single-output discrete time closed-loop control system. Indirectly, a discrete time control system can be designed from the equivalent continuous time control system via transform method. Also it can be designed directly using root locus method, frequency response method, or analytical

method. Where there is deficiency in the root locations or frequency response of the plant, compensation would be needed to obtain the desired root locations or frequency response.

The indirect design method via transform requires the design of a conventional continuous time control system first and then translates it into discrete time form. The methods available for the translation include pole-zero mapping, impulse invariance method and numerical integration such as and bilinear transformation method. The root locus method is based on the pole-zero configuration in the z-plane. By adding new poles or zeros to compensate or cancel the undesirable plant poles or zeros, the desired transient and steady state performance of the control system would therefore be achieved. While the frequency response method gives opportunity to design a control system whose specifications are given in frequency domain. However, the analytical method is quite different from the above elementary methods, it is based on the idea that all aspects of the performance of a closed-loop control system might be measured by a single, suitably defined, performance criterion. Essentially, a performance index is used in this design method to measure the performance of the system control. The analytical method is widely used in optimal control and stochastic control.

In design of a control system, in order to obtain a control system that meets all the given specifications, it is quite common for us to finish the design via trial-and-error approach. The general procedure of designing a discrete time control system via this approach involves choosing an appropriate control strategy, designing the controller, setting up the mathematical model of the closed-loop system, constructing a prototype and simulating the system. Once the satisfactory performance has been obtained from the computer simulation, the system should be tested via experiment in real environment. If the performance does not satisfy the specifications, which is likely to happen because of the imperfect plant modelling (such as nonlinearities etc.) that the original design does not take into consideration, changes must be made on the prototype until the system meets the specifications.

3.2.2. Transient and Steady State Analysis

Absolute stability of a control system is defined as whether or not the output of the system eventually comes back to its equilibrium state when the system is subjected to a disturbance. In equilibrium, a control system maintains the same output in the absence of any disturbance or input. In analysing and designing of a closed-loop control system, the dynamic behaviour of the system must be predictable, and absolute stability of the system is the most important characteristic of the dynamic behaviour. Using test signals, the absolute stability and performance of a control system can be easily tested. Step functions and impulse functions are

two of the commonly used test signals.

With impulse signal input to the control system, the absolute stability of the control system can be tested. For the unit impulse signal $x(t) = \delta(t)$, due to $X(z)=1$, then the z-transform of the impulse response of the control system is:

$$Y(z) = G(z)X(z) = G(z)$$

and $y(k)$, which is the inverse z-transform of $Y(z)$, is the impulse response.

While with impulse signal, the response of a closed-loop control system to a transient disturbance can be tested when the system is at equilibrium state, we can explore the transient response and steady state response of a closed-loop control system with a step input signal.

The z-transform of the output of the closed-loop control system can be obtained as follows:

$$Y(z) = G(z)X(z) = \frac{z}{z-1}G(z)$$

and the inverse z-transform of $Y(z)$ is the step response of the closed-loop control system.

For example, for a control system, shown in Figure 3-3, having a following closed-loop pulse transfer function

$$G(z) = \frac{H(z)}{1+H(z)} = \frac{2.491\times10^{-5}(1+2z^{-1}+z^{-2})}{1-1.9929z^{-1}+0.993z^{-2}} \qquad (3\text{-}5)$$

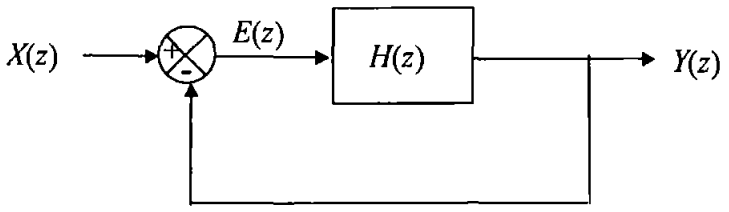


Figure 3-3 An example closed-loop control system

The impulse response and step response of the example closed-loop control system is shown in Figure 3-4 and Figure 3-5, respectively.

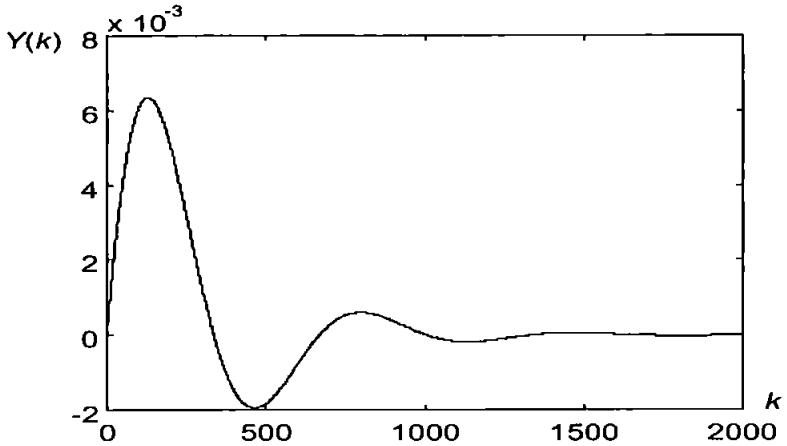


Figure 3-4 Impulse Response of the example Closed-loop System

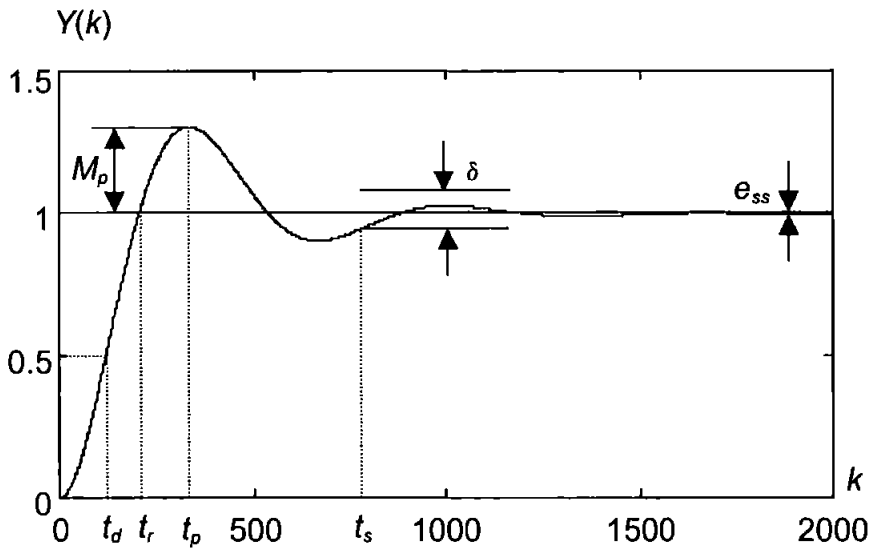


Figure 3-5 Step Response of the example Closed-loop System

The impulse response of the system shows that the output of the control system will eventually stay at its equilibrium state, which is 0, following the stimulation of the unit impulse signal at time 0. Such a system response will be superposed to the overall system output of any linear closed-loop control system at any time when the system is suffered from a unit impulse disturbance.

The step response of the system shown in Figure 3-5 indicates the transient and steady state response of the system to a fixed target signal. From Figure 3-5, a set of system specifications in time domain can be defined.

Transient Response Analysis

The transient response of the system to the step input defines the delay time (t_d), rise time (t_r), peak time (t_p), settling time (t_s), the maximum overshoot (M_p) and the damping ratio (ζ). Figure 3-6 shows the relationship between the damping ratio (ζ) and other transient time parameters in second order discrete time systems that have different values of damping ratio. The transient response shows the speed with which the system enters into its steady state.

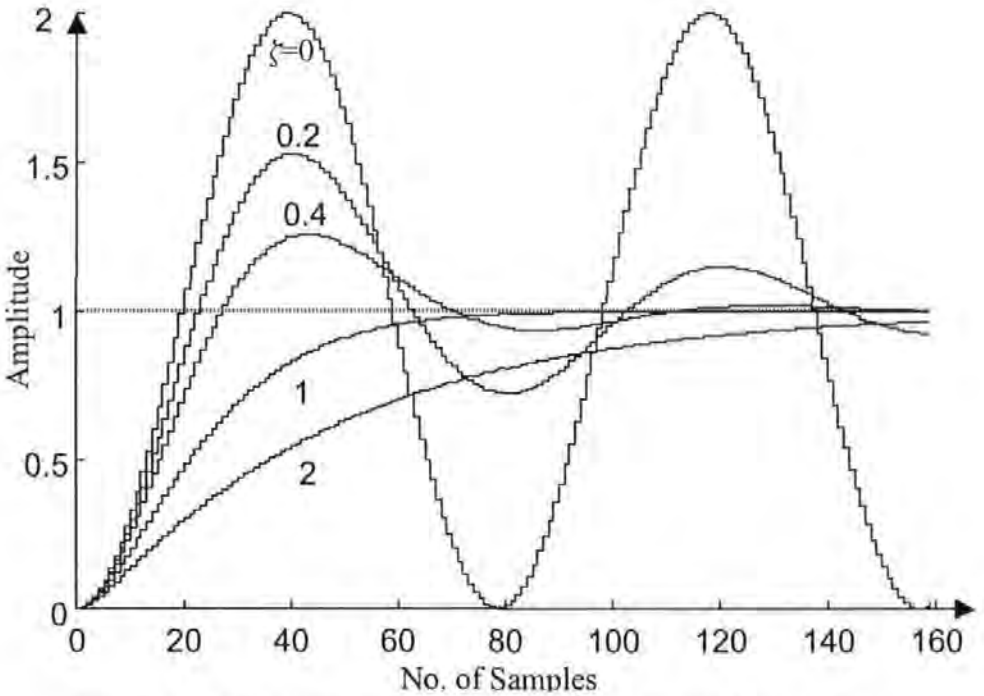


Figure 3-6 Step responses of second order discrete time systems
(natural frequency w_n=0.8, sampling period T=0.1s, damping ratio ζ=0~2)

Steady State Error Analysis

The steady state response of the system to the step input specifies the allowable tolerance (δ) and the steady state error (e_{ss}). The steady state response demonstrates how well the system

maintains its steady state.

By use of the final value theorem, the steady state error of the discrete time control system shown in Figure 3-3 can be expressed as

$$e_{ss} = \lim_{k\to\infty} e(k) = \lim_{z\to 1}(1 - z^{-1})E(z)$$

or

$$e_{ss} = \lim_{z\to 1} \frac{(1 - z^{-1})}{1 + H(z)} X(z)$$

when the input of the system is unit step $u(k)$, unit ramp $ku(k)$, or unit acceleration signal $k^2u(k)$, respectively, the steady state error can then be obtained

$$e_{ss} = \frac{1}{1 + K_p} \qquad \text{for unit step input} \qquad (3\text{-}6)$$

$$e_{ss} = \frac{1}{K_v} \qquad \text{for unit ramp input} \qquad (3\text{-}7)$$

$$e_{ss} = \frac{1}{K_a} \qquad \text{for unit acceleration input} \qquad (3\text{-}8)$$

where $K_p = \lim_{z\to 1} H(z)$ is static position error constant, $K_v = \lim_{z\to 1} \frac{1 - z^{-1}}{T} H(z)$ is static velocity error constant, and $K_a = \lim_{z\to 1} \frac{(1 - z^{-1})^2}{T^2} H(z)$ is static acceleration error constant.

For type 0 system (in which there is no open loop pole at z=1), the steady state error in response to unit step input is finite. For type 1 system (in which there is one open loop pole at z=1), the steady state error is zero in response to unit step input, but finite to unit ramp input. For type 2 system (in which there are two open loop poles at z=1), the steady state error is zero in response to both unit step and unit ramp input whereas finite in response to acceleration input.

For example, the steady state error of the example system in response to the unit step input is

and $1 + H(z) = \frac{1}{1 - G(z)}$, therefore the steady state error of the example closed-loop system is

$$e_{ss} = \lim_{z \to 1} \frac{1}{1 + H(z)} = \lim_{z \to 1} (1 - G(z)) = 0.0036$$

and the static position error constant is

$$K_p = \frac{1}{e_{ss}} - 1 = 276.8$$

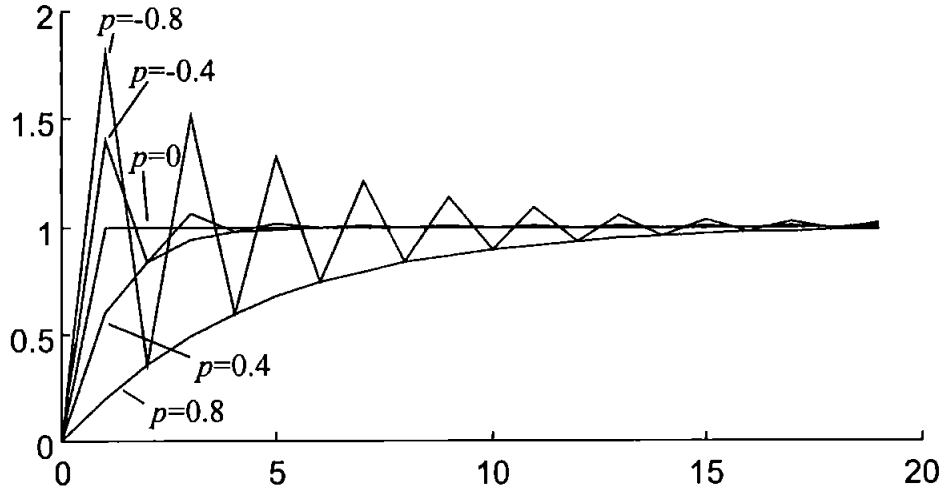
3.2.3. Root Locus Analysis

The basic characteristic of the transient response of a closed-loop control system depends very much upon the location of the poles of the closed-loop pulse transfer function, i.e., $G(z)$, especially if the system has a variable open loop gain that varies the location of the closed-loop poles. It is important for such a closed-loop system to choose gains that make the system stable. In order to choose the right gains for the closed-loop system, it is necessary to investigate the root locus of the system when the loop gain varies. On the other hand in the design of a closed-loop system with fixed gain, one may obtain an appropriate gain by moving the location of the poles to better or the desired location so as to improve the transient response characteristic of the closed-loop system.

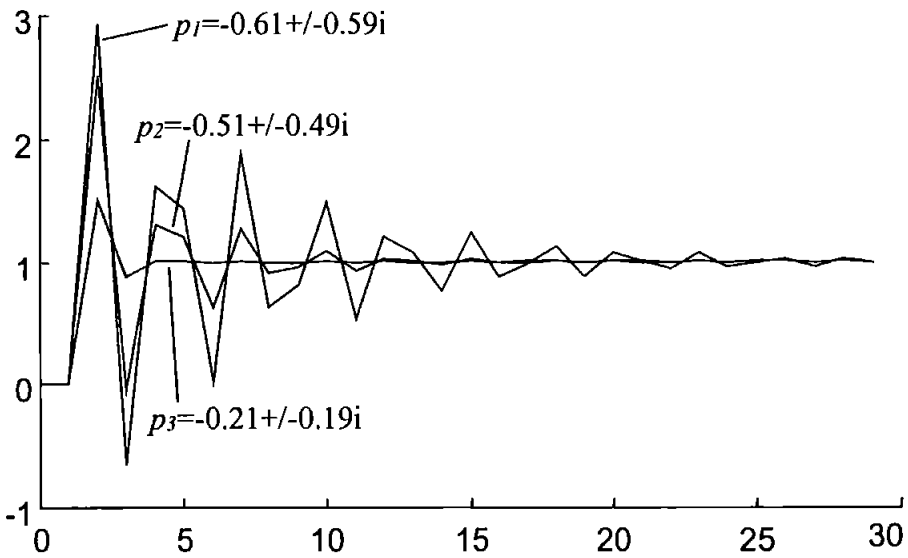
According to equation (3-2), the closed-loop poles are the roots of the following characteristic equation:

$$1 + H(z) = 0 \qquad (3\text{-}9)$$

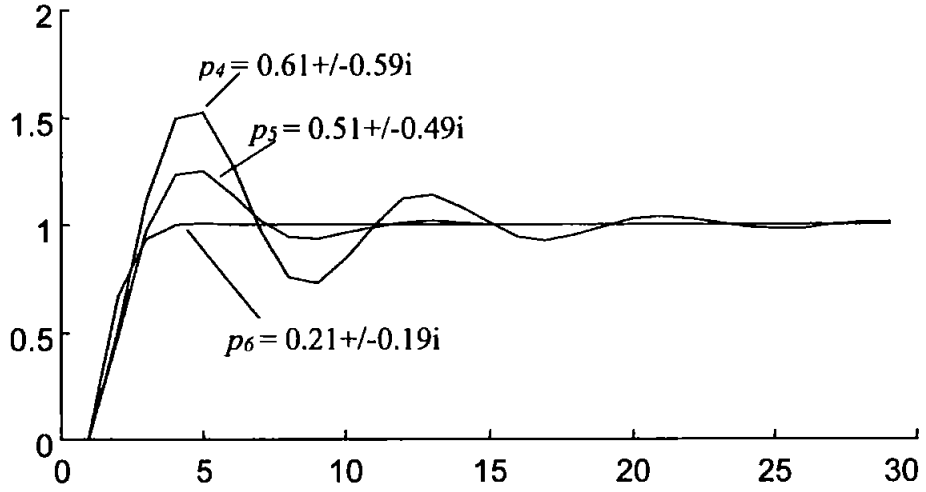
$H(z)$ is the open-loop pulse transfer function. When the gain of $H(z)$ varies, the roots of equation (3-9) will consequently be changed. The relationship between the pole location and the transient response of the closed-loop control system is shown in Figure 3-7. All the poles of a stable closed-loop system are within the unit circle. A pole at origin allows the output of the closed-loop system following the system input with one cycle time delay, however when the pole is in a place within the unit circle other than the origin, it will cause the system output either damped or oscillatory. Any pole outside the unit circle will cause the system unstable. Positive real pole makes the system response sluggish whereas the negative real pole causes it oscillatory (Figure 3-7 (a)). Generally, all complex conjugate pole pairs make the system response oscillatory, the closer pole pair to the unit circle will result in more oscillatory in system response. See Figure 3-7 (b) and (c) for the system responses caused by the poles whose locations are shown in Figure 3-7 (d) in the complex plane.



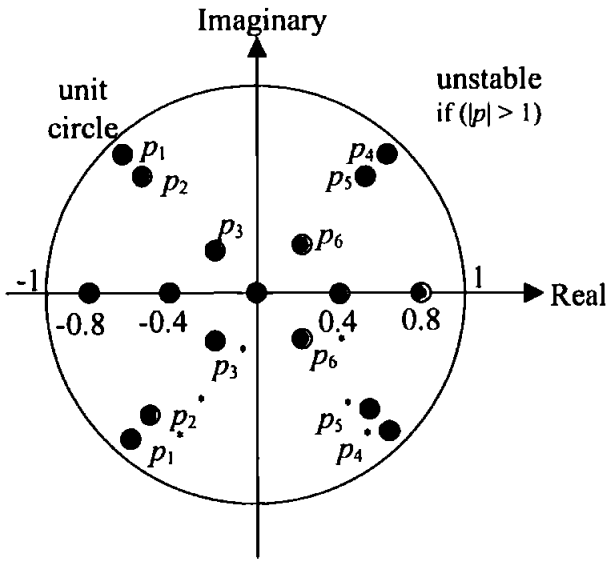
(a) Step responses from a single real pole



(b) Step responses from a pair of complex conjugate poles in left half plane



(c) Step responses from a pair of complex conjugate poles in right half plane



(d) Location of the poles in complex plane

Figure 3-7 The effect of pole Location on transient response of closed-loop systems
(p represents a pole of a closed-loop system. p_i and p_i^* are complex conjugate pole pair.)

3.2.4. Frequency Response Analysis

The frequency response concept of closed-loop control systems is very useful for the analysis and design of either continuous time or discrete time systems. As the same for continuous time system analysis, the frequency response analysis of discrete time control systems is based on the Bode diagram that consists of two separate plots: the logarithmic magnitude of the open-loop transfer function ($-20\log|H(w)|$) versus logarithmic frequency, and its phase

angle ($\angle H(w)$) versus logarithmic frequency.

Because in the z-plane the frequency appears as $z = e^{jwT}$, if we apply the conventional frequency response analysis in the z-plane, the simplicity of the logarithmic plots will be completely lost. Furthermore, since the z-transformation maps each strip of the left half s-plane into the interior of the unit circle in the z-plane (Figure 3-8), the conventional frequency response methods that are based on the entire left half plane does not apply to the z-plane. However, the difficulty can be overcome by transforming the pulse transfer function from z-plane into w-plane using the so-called w-transformation. The w-transformation is a bilinear transformation and is defined by

$$z = \frac{1 + (T/2)w}{1 - (T/2)w} \tag{3-10}$$

where T is the sampling period. The inverse relationship between z and w is

$$w = \frac{2}{T}\frac{1 - z^{-1}}{1 + z^{-1}} \tag{3-11}$$

This transformation is graphically shown by Figure 3-8. After the pulse transfer function $H(z)$ is w-transformed into $H(w)$, the conventional frequency response methods can be applied to the analysis and design of discrete time control systems.

Figure 3-9 shows the Bode diagram for the follow transfer function

$$H(z) = 0.1018\frac{z + 0.9356}{z^2 - 1.5071z + 0.5071}$$

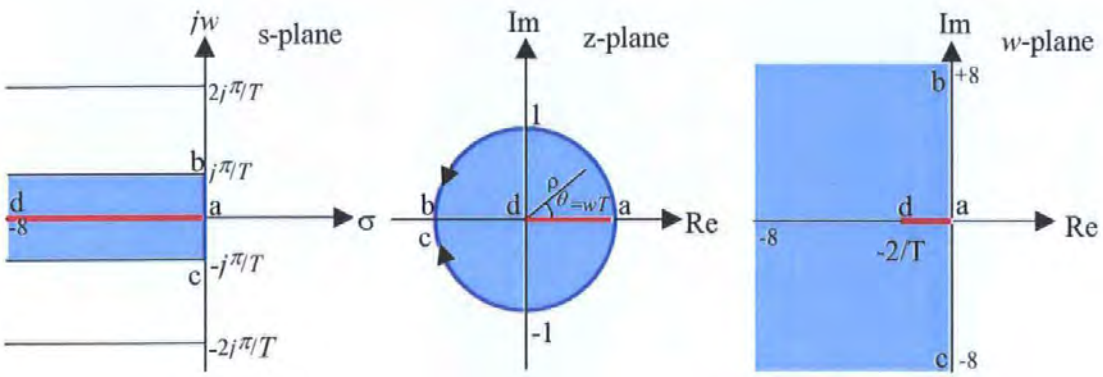


Figure 3-8 Mappings between s-plane, z-plane, and w-plane

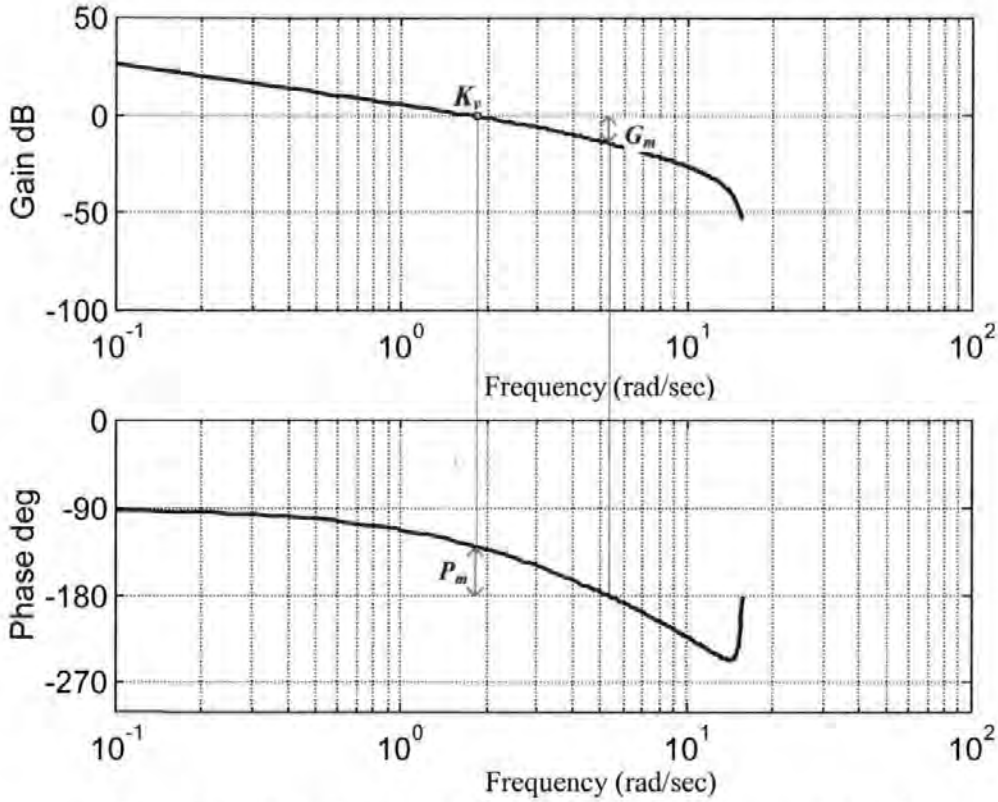


Figure 3-9 Bode diagram for the given transfer function in w-plane

In a Bode diagram, the gain margin G_m is defined as the magnitude of $H(w)$ at some frequency at which its phase is 180°; while the phase margin P_m is defined as the phase of $H(w)$ at some frequency at which its magnitude is 0dB; the resonant frequency F_r is the frequency at which there is a peak value for the magnitude of $H(w)$. For type 0 systems, the static position error constant K_p can be read indirectly from the magnitude plot of a Bode diagram, because low frequency asymptote is a horizontal line that intersects with w=0 line at $20\log K_p$ dB. For type 1 systems, the intersection of the initial –20dB/decade segment (or its extension) with the 0dB line has a frequency numerically equal to K_v . Finally, for the static acceleration error constant K_a, the intersection of the initial –40dB/decade segment (or its extension) with the w=1 line has the magnitude of $20\log K_a$. From the Bode diagram shown in Figure 3-9, we can read G_m=14dB, P_m=50, and K_v=1.8, however K_p, K_a, and F_r are not available from this Bode diagram.

3.2.5. Bilinear Transformation

Transform method can be applied to translate a transfer function representing a continuous time system to its equivalent pulse transfer function representing a discrete time system, we can therefore use this technique to design a discrete time controller if its equivalent continuous time controller is already available, and bilinear transformation method is one of the popular techniques used in control system designs.

Bilinear transformation method is a numerical integration method that uses the following mapping equation to discretize a continuous time system represented by a transfer function in s- plane:

$$s = \frac{2}{T}\frac{1-z^{-1}}{1+z^{-1}}, \text{ where T is the sampling period} \qquad (3\text{-}13)$$

This mapping method is based on the area approximation by trapezoidal integration illustrated by Figure 3-10 where the area under $y(t)$ between 2T and 3T is approximated by the shaded rectangle area:

$$\int_{2T}^{3T} y(t)dt = \frac{y(2T)+y(3T)}{2}T$$

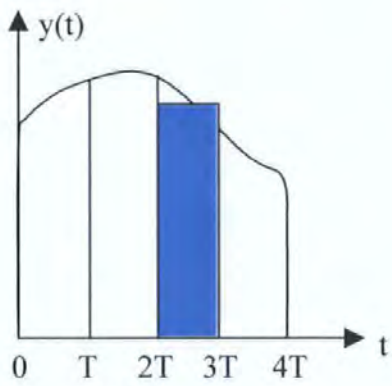


Figure 3-10 Approximation of area calculation by trapezoidal integration

Extend this method to each sampling interval, the whole area under $y(t)$ could be approximately calculated as follow

$$\int_0^t y(t)dt = \sum_{n=1}^{k} \frac{T}{2}[y((n-1)T) + y(nT)] \qquad (3\text{-}38a)$$

applying z-transformation on both sides, then

$$\square\,[\int_0^t y(t)dt] = \frac{T}{2}\frac{1+z^{-1}}{1-z^{-1}} \qquad (3\text{-}38b)$$

As shown in Figure 3-11, the equation (3-13) maps the entire left half s-plane into the area inside the unit circle in z-plane, and the entire imaginative axis in s-plane into one complete revolution of the unit circle in z-plane.

However, due to the possible high frequency distortion, the bilinear transformation is usually used with frequency prewarping by replacing the frequency (a in equation (3-12), for example) with $\frac{2}{T}\tan\frac{aT}{2}$.

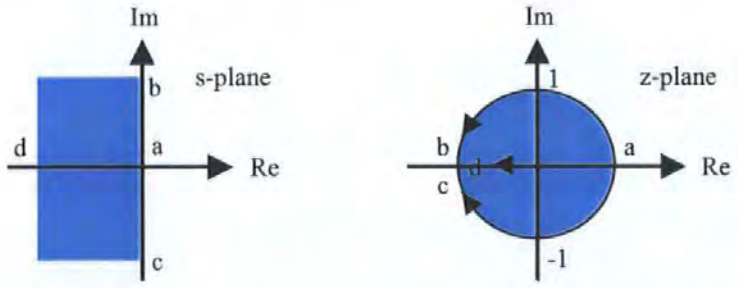


Figure 3-11 Mapping between s-plane and z-plane by bilinear transformation
(points b, c, and d in s-plane are in infinity, whereas in z-plane they approach (-1,0))

By using the bilinear transformation and prewarping method, the analog system represented by the equation (3-12) can be converted into a discrete time system represented by the following pulse transfer function

$$\frac{(1+z^{-1})\tan\frac{aT}{2}}{1+\tan\frac{aT}{2}-(1-\tan\frac{aT}{2})z^{-1}}$$

3.2.6. System Compensation

3.2.6.1.Phase Lead Compensation

As stated earlier, $H_c(s)$ hence $H_c(z)$ is a phase lead compensator if $T_1 > T_2$. The Bode diagram of this compensator is shown in Figure 3-12.

From the Bode diagram, it can be seen that the phase lead compensator has little effect on the frequency response at low frequencies, but improves the high frequency response, or transient response, so that larger gain can be used, with consequent improvement in steady state performance.

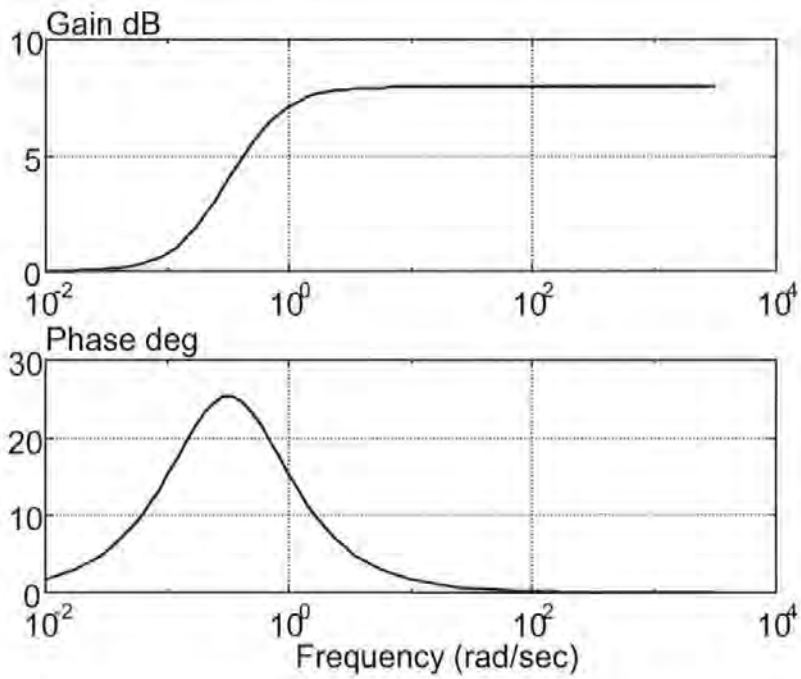


Figure 3-12 Bode diagram of a phase lead compensator (T=0.001s, T_1=5, T_2=2)

Phase lead compensation is commonly used for improving stability margins and increasing the system bandwidth. Thus, the system has a faster transient response speed or a shorter settling time. However, its increased high frequency gains may be subjected to high frequency noise problems.

3.2.6.2.Phase Lag Compensation

When $T_1 > T_2$, $H_c(s)$ hence $H_c(z)$ is a phase lag compensator, the Bode diagram of this

compensator is shown in Figure 3-13.

Phase lag compensation reduces the system gain at higher frequencies, therefore high frequency noises involved in the system can be attenuated, or the total system gain can be increased and thereby low frequency gain can be increased and the steady state accuracy can be improved. However, the phase lag compensator reduces the system bandwidth, which slows down the system response speed.

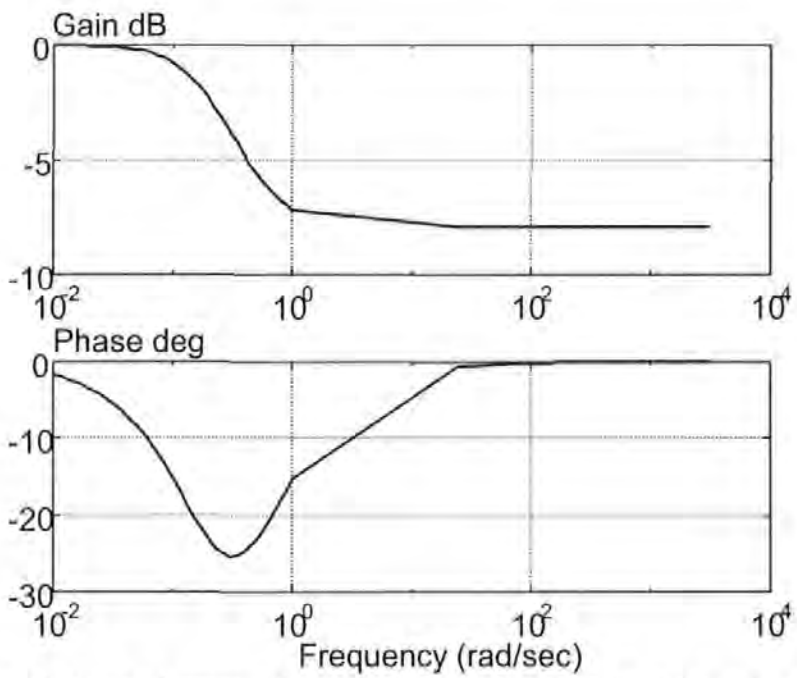


Figure 3-13 Bode diagram of a phase lag compensator (T=0.001s, T_1=2, T_2=5)

3.2.6.3.Phase Lag-Lead Compensation

Phase lead and phase lag compensations improve overall performance in different ways. One is designed to improve the high frequency, or transient, response of the controlled process; the other is designed to improve its low frequency, or steady state, response. There is little interaction between the effects of the two and so both can be used together, in the same controller, with advantage. By cascading the phase lead compensator and the phase lag compensator above with little modification, a typical phase lag-lead compensator would be obtained

$$H_c(s) = \frac{1+sT_1}{1+sT_1\alpha}\frac{1+sT_2}{1+sT_2\beta} \quad (\alpha<1, \beta>1) \qquad (3\text{-}15)$$

A Bode diagram of this lag-lead compensator is shown in Figure 3-14.

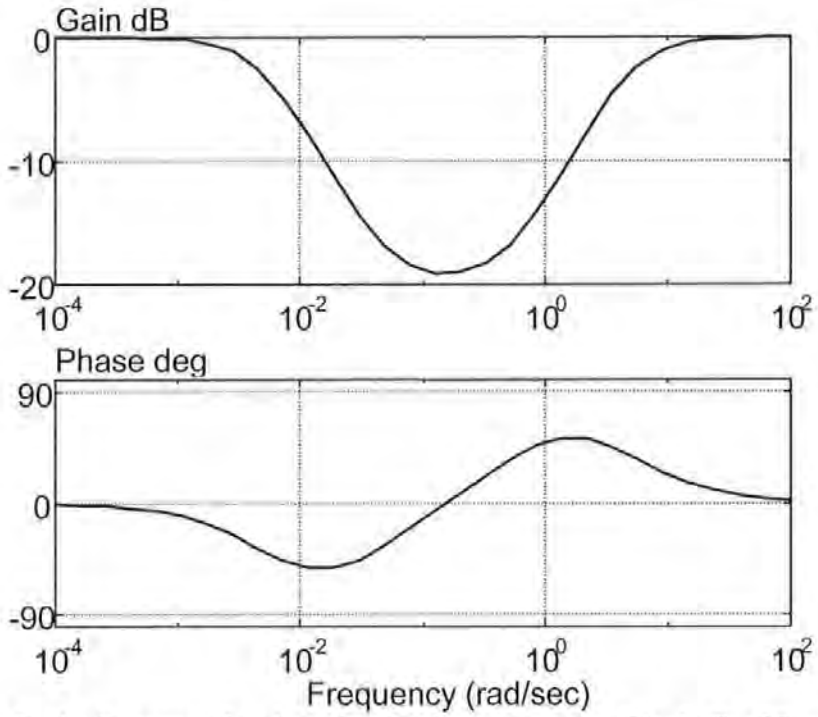


Figure 3-14 Bode diagram of a phase lag-lead compensator (T_1=2, T_2=20, α=0.1, β=10)

3.2.7. PID Control

3.2.7.1.Introduction

PID control has been successfully used in industry and many other areas over years due to its simplicity, quick response and efficiency. For a control object that has some unknown dynamics, or its non-linearity is not small enough to be ignored, PID control is usually a common choice for start by offering satisfactory results.

For a drug infusion control system, response speed is the most important requirement, and quick response is one of the main advantages of a PID controller. The simplicity of a PID controller reduces significantly the requirement from computational resources for a closed-loop anaesthesia system.

Fuzzy control, neural network control and adaptive control have also been used in closed-loop anaesthesia control. However a large database has to be built before it could be used for closed-loop anaesthesia investigation using fuzzy logic control, while adaptive control and

neural network control have much slower response speed with heavy demand on computational capability.

3.2.7.2.PID Control Law

As suggested by its name, PID control consists of three control actions: proportional control, integral control, and derivative control, K_p, K_i, and K_d are known as the gains of these control actions, respectively. The PID controller acts on an error signal e(t), the proportional control simply multiplies the error with a constant; the integral control multiplies the integral of the error signal, or the accumulated error; whereas the derivative control multiplies the time derivative of the error signal, or the rate of change of the dynamic error. The integral control is introduced in the PID controller for reducing the steady state error, while the derivative control is to provide an anticipatory action to suppress the overshoots or undershoots in the response. Various type of PID control can be seen in industry or other areas, however, PI (proportional integral), PD (proportional derivative), and PID are the most commonly used PID type controllers.

The PID control law and its s-domain transfer function are shown in (3-16) and (3-17).

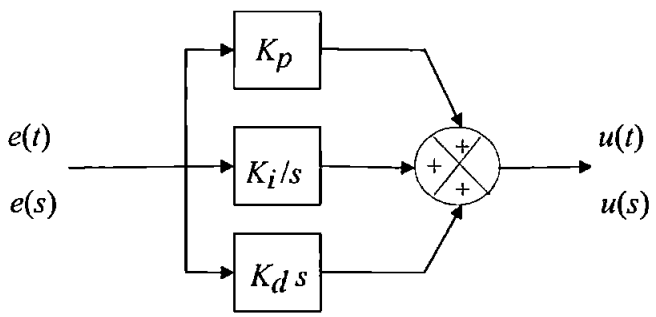


Figure 3-15 A continuous PID controller

$$u(t) = K_p e(t) + K_i \int_0 e(t)dt + K_d \frac{de(t)}{dt} \tag{3-16}$$

$$H_c(s) = K_p + \frac{K_i}{s} + K_d s \tag{3-17}$$

In order to obtain the pulse transfer function for the discrete time controller, we can discretize the equation (3-16). The integration term in (3-16) can be approximated using trapezoidal

integration shown in equation (3-14) and Figure 3-10, while the derivative term can be discretized by a two- point difference as shown in (3-18) and (3-19):

$$u(kT) = K_p e(kT) + K_i \sum_{n=1}^{k} \frac{T}{2}[e((n-1)T) + e(nT)] + K_d \frac{e(kT) - e((k-1)T)}{T} \quad (3\text{-}18)$$

The z-transformation on (3-18) gives

$$u(z) = (K_p + K_i \frac{T}{2}\frac{1+z^{-1}}{1-z^{-1}} + K_d \frac{1-z^{-1}}{T})e(z) \quad (3\text{-}19)$$

Hence the discrete time PID controller pulse transfer function is

$$H_c(z) = K_p + K_i \frac{T}{2}\frac{1+z^{-1}}{1-z^{-1}} + K_d \frac{1-z^{-1}}{T} \quad (3\text{-}20)$$

From the continuous time transfer function of PID controller in equation (3-17), we know PID controller is a special case of a phase lag-lead controller. In fact, if we cascade a simple phase lag compensator $K_1(1+sT_1)$, which is basically a PD controller, and a simple phase lead compensator $K_2(1+\frac{1}{sT_2})$, which is a PI controller, we obtain a phase lag-lead compensator having the following transfer function

$$H_c(s) = K_1(1+sT_1)K_2(1+\frac{1}{sT_2}) = (K_1K_2 + \frac{K_1K_2T_1}{T_2}) + \frac{K_1K_2}{sT_2} + sK_1K_2T_1$$

$$H_c(s) = K_p + \frac{K_i}{s} + K_d s$$

This has the same transfer function as the PID controller, here $K_p = K_1K_2(1+\frac{T_1}{T_2})$, $K_i = \frac{K_1K_2}{T_2}$, and $K_d = K_1K_2T_1$.

As a phase lead compensator, the PD control action affects the high frequency region, increases the phase lead angle and improves system stability as well as increasing the system bandwidth (and thus improving the transient response). As a phase lag compensator, the PI control action affects the low frequency portion, increases the low frequency gain and improves steady state accuracy. The PID control action is a combination of the PI and PD control actions.

3.3. *Higher Order Spectra*

3.3.1. Introduction

Spectral analysis has been widely used in digital signal processing to extract important information that is "hidden" in the digital signal or data series. One of the most fundamental and useful tools for this purpose has been the estimation of the power spectrum of discrete-time deterministic and stochastic processes. In power spectrum estimation, the process under analysis is assumed as a superposition of statistically unrelated harmonic components and the distribution of power among these frequency components is then estimated. However, power spectral analysis investigates only the linear relationship between the frequency components and suppresses their phase relations.

The power spectrum provides the statistical description of a Gaussian process of known mean. In real world, it is common for a practical process, such as EEG signal, to deviate from Gaussianness or normality and to contain non-linearities, and this "hidden" information is extractable from estimating higher order spectrum such as bispectrum.

Higher order spectra are defined in terms of higher order cumulants of a process. Suppose $\{X(k)\}$ is a real stationary random process with zero mean (i.e., $E\{X(k)\}=0$), the Nth-order spectrum $C(\omega_1,\omega_2,...,\omega_{N-1})$ of the process $\{X(k)\}$ is defined as the Fourier transform of its Nth-order cumulant sequence $c_N(\tau_1,\tau_2,...,\tau_{N-1})$:

$$C(\omega_1,\omega_2,...,\omega_{N-1})=\sum_{\tau_1=-\infty}^{+\infty}\cdots\sum_{\tau_{N-1}=-\infty}^{+\infty}c_N(\tau_1,\tau_2,...,\tau_{N-1})e^{-j(\omega_1\tau_1+...+\omega_{N-1}\tau_{N-1})} \qquad (3\text{-}21)$$

An important property for higher order spectra is that all higher order ($N \geq 3$) spectra are zero for a stationary Gaussian process.

Power spectrum and bispectrum are both the members of higher order spectra. By definitions, power spectrum is the second order spectrum while bispectrum is the third order spectrum.

3.3.2. Power Spectrum

Power spectrum has been used in a wide range of application areas such as bioengineering and telecommunication. If $x(k)$ is a real, discrete, and zero-mean stationary random process, the autocorrelation sequence $r(\tau)$ and power spectrum $P(\omega)$ of this process are defined as

$$r(\tau)=E\{x(k)x(k+\tau)\} \qquad (3\text{-}22)$$

$$P(\omega)=\sum_{\tau=-\infty}^{+\infty} r(\tau)e^{-j\omega\tau}, \qquad |\omega|<\pi \tag{3-23}$$

where E denotes expectation. Equation (3-23) demonstrates that power spectrum is a special member of higher order spectra with N=2 as shown in (3-24)

$$C(\omega_1)=\sum_{\tau_1=-\infty}^{+\infty} c_2(\tau_1)e^{-j\omega_1\tau_1} \tag{3-24}$$

Power spectrum characterises the power distribution of the process $x(k)$ over its frequency components, and all non-linear characteristics within this process is suppressed during the power spectrum estimation.

Consider the following processes (Nikias and Raghuveer, 1987)

$$x_1(k)=\cos(\lambda_1 k+\varphi_1)+\cos(\lambda_2 k+\varphi_2)+\cos(\lambda_3 k+\varphi_3) \tag{3-25}$$

$$x_2(k)=\cos(\lambda_1 k+\varphi_1)+\cos(\lambda_2 k+\varphi_2)+\cos(\lambda_3 k+\varphi_1+\varphi_2) \tag{3-26}$$

where $\lambda_3=\lambda_1+\lambda_2$ (which means $\lambda_1,\lambda_2,\lambda_3$ are harmonically related), and $\varphi_1,\varphi_2,\varphi_3$ are independent random variables uniformly distributed within [0, 2π]. In (3-25), λ_3 is an independent harmonic component because ϕ_3 is an independent random phase variable, whereas in (3-26) it is a result of phase coupling between λ_1 and λ_2. The power spectrum of $x_1(k)$ and $x_2(k)$ are demonstrated in Figure 3-16.

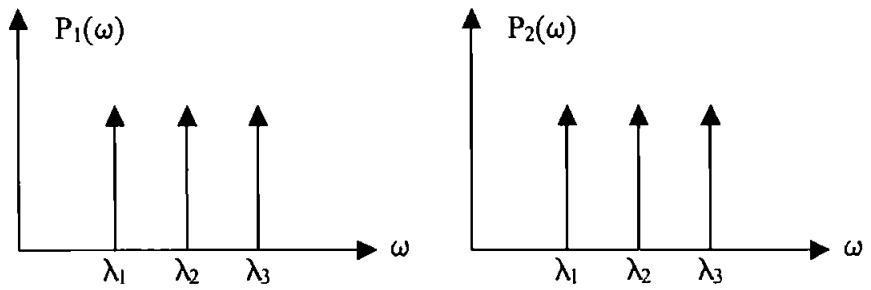


Figure 3-16 Power spectrum of processes $x_1(k)$ (without phase coupling) and $x_2(k)$ (with quadratic phase coupling) shown in (3-25) and (3-26)

3.3.3. Bispectrum

Bispectrum, like power spectrum, is a special member of higher order spectra with N=3. If $x(k)$ is a real, discrete, and zero-mean stationary random process, the bispectrum $B(\omega_1,\omega_2)$ of this process is defined as

$$B(\omega_1,\omega_2)=\sum_{m=-\infty}^{+\infty}\cdots\sum_{n=-\infty}^{+\infty}R(m,n)e^{-j(\omega_1 m+\omega_2 n)} \tag{3-27}$$

where $R(m,n)$ is the third order moment or cumulant sequence of $x(k)$, and is defined as

$$R(m,n)=E\{x(k)x(k+m)x(k+n)\} \tag{3-28}$$

From the definition of bispectrum in (3-27) and (3-28), the following properties of bispectrum can be identified

- $B(\omega_1,\omega_2)$ is generally complex, i.e., $B(\omega_1,\omega_2)=\mid B(\omega_1,\omega_2)\mid e^{j\psi(\omega_1,\omega_2)}$
- $B(\omega_1,\omega_2)$ is periodic with a period of 2π, i.e., $B(\omega_1,\omega_2)=B(\omega_1+2\pi,\omega_2+2\pi)$
- $B(\omega_1,\omega_2)$ is symmetry with

$$B(\omega_1,\omega_2)=B(\omega_2,\omega_1)=B^*(-\omega_2,-\omega_1)=B^*(-\omega_1,-\omega_2)=B(-\omega_1-\omega_2,-\omega_2)$$

$$=B(\omega_1,-\omega_1-\omega_2)=B(-\omega_1-\omega_2,\omega_1)=B(\omega_2,-\omega_1-\omega_2)$$

These properties indicate that the bispectrum in the triangular region of $\omega_2\geq 0$, $\omega_1\geq\omega_2$, and $\omega_1+\omega_2\leq\pi$ (within region I in Figure 3-17) is enough to completely describe the bispectrum of a process.

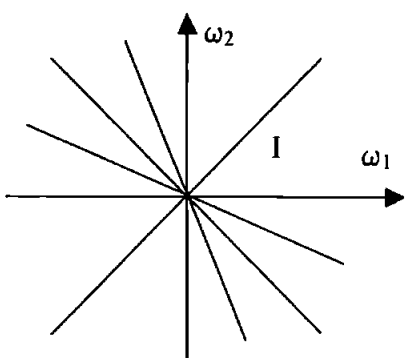


Figure 3-17 The symmetry property of bispectrum

For example, because of quadratic non-linearity, phase coupling between two frequency components of a process will have a contribution to the power at the frequency which is equal to their sum. Such phase coupling affects the third order cumulant or moment sequence and therefore bispectrum can be used to detect and characterise the non-linearity in the process.

In the previous example processes defined in (3-25) and (3-26), the power spectral analysis regarded the both processes to carry the same information and failed to detect the quadratic phase coupling in the process $x_2(k)$. However, the bispectrum analysis on the same processes reveals successfully the non-linearity contained in the process $x_2(k)$. As shown in Figure 3-18, the bispectrum of $x_1(k)$ is zero whereas that of $x_2(k)$ shows an impulse at $\omega_1=\lambda_1$ and $\omega_2=\lambda_2$ (if $\lambda_1 \geq \lambda_2$) within the triangular region defined by $\omega_2 \geq 0$, $\omega_1 \geq \omega_2$, and $\omega_1 + \omega_2 \leq \pi$.

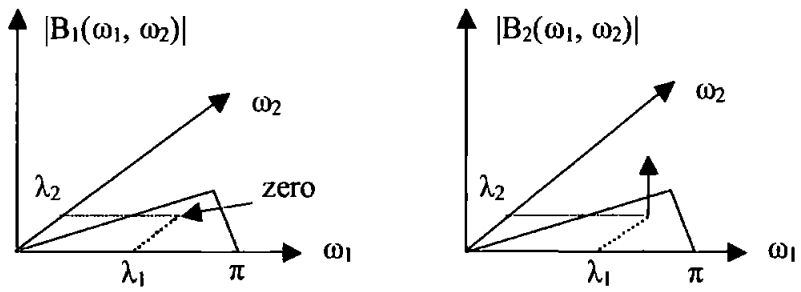


Figure 3-18 Bispectrum of processes $x_1(k)$ (without phase coupling) and $x_2(k)$ (with quadratic phase coupling) shown in (3-25) and (3-26)

This example has well demonstrated the capability of bispectrum in detecting and characterising the non-linearity of a system that has lead to its application in many areas including the analysis of EEG signal.

3.3.4. EEG Application

As introduced in Section 2.2.3, the EEG signal is a waveform representing the electrical activity of the brain. In particular, the bioelectrical activity of millions of neurons in the brain contributes to the information of an EEG signal with very complex non-linear dynamics. Embedded in that signal is information regarding frequency, amplitude and phase interactions

which change as the neuronal firing patterns change. As a result, the properties of the EEG may be significantly altered by anaesthetics, neuroactive drugs, hypothermia, and other physiologic changes that affect cerebral function. Hence the assessment of a patient's brain state during surgery has long been an objective of research in the field of EEG analysis.

Like any other signals, the EEG signal can be broken down into a set of sine wave components such that when the components are combined together, the original signal is recovered. Traditionally, power spectral analysis is used to decompose the EEG signal and obtain the amplitudes or power of the sine wave components. A set of EEG-derived power spectral variables have been used to identify the anaesthetic states, such as median frequency (MF) and spectral edge frequency (SEF).

However, as introduced previously, by using power spectral analysis on the EEG signal, one is implicitly making assumption that each sine wave component of the EEG waveform is independent and there are no relationships between the sine wave components. This is not true as almost all biological system, including the brain, exhibit non-linear behaviour and inter-component relationships are typically present in the signals generated by such non-linear systems. Therefore, an analysis technique that can detect and quantify non-linear changes of the EEG signal is needed to obtain a better estimation on anaesthetic states, and among them is the bispectral analysis.

3.3.4.1.Median Frequency

Median frequency is defined as the frequency below which it lies half of the power in the EEG waveform. By applying Fourier transformation on the EEG waveform, the contribution from each sine wave component to the total power of the EEG waveform can be easily calculated, and then the median frequency can be determined.

Median frequency has been evaluated extensively by Schwilden, Schuttler and colleagues. They found (Schwilden, Stoeckel and Schuttler, 1989) by clinical experiments that during pre-anaesthetic base-line conditions, median frequency centred around 10Hz, while during anaesthesia its contribution was confined to below 5Hz, and after the patients had responded to verbal commands in the recovery period, the median frequency stayed above 6Hz. Based on their findings, they concluded that median frequency of below 5Hz should be maintained when aiming at non-responsiveness to verbal commands during anaesthesia, and that the optimal range of median frequency is 2-4Hz to achieve a probability of 5% or less for the occurrence of signs of undue anaesthesia. They have implemented an adaptive closed-loop

system using median frequency feedback with the target median frequency of 2-3Hz (Schwilden, Schuttler and Stoeckel, 1987), and a number of clinical experiments have been done with the system using different drugs (Schwilden, Schuttler and Stoeckel, 1987; Schwilden, Stoeckel and Schuttler, 1989; Schwilden and Stoeckel, 1993; Schuttler et al., 1995). It is reported that median frequency of 2-3Hz offers a level of anaesthesia sufficient to ensure unconsciousness (Schwilden, Schuttler and Stoeckel, 1987). However, to achieve this target, they had to stimulate the subjects every 1.5 minutes with six different acoustic and tactile stimuli so that higher drug concentration could be maintained with the same median frequency target. Another deficiency in using median frequency is that it is greatly affected by filtering and in particular, by the high-pass filter frequency. Furthermore, it is reported that there was no recorded value for median frequency that was 100% specific for unconsciousness and it is poorly correlated with blood concentration of propofol (Gajraj et al., 1998).

3.3.4.2.Auditory Evoked Response

As stated in (Thornton and Newton, 1989): The auditory evoked response is the response in the EEG to a sound stimulus. It is extracted from the EEG by computer averaging, and consists of a series of waves representing the passage of electrical activity along the auditory pathway from the cochlea through the brain-stem to cortex. The auditory evoked response has three phases which are brain-stem response, early cortical response and late cortical response. Although AER is useful for assessing the depth of anaesthesia, which AER parameter is the best measure of the DOA remains controversial. The Kenny group (1992) uses an AER index, called LAS (level of arousal score), as the measure of the DOA in their CLAN system. They found that LAS appears to distinguish the awake from asleep state (Doi et al., 1997), to give more consistent values when using different anaesthetic agents (Schraag et al., 1998), and that LAS is the best index, in comparison with BIS, MF and SEF95, to distinguish the transitions from consciousness to unconsciousness (Gajraj et al., 1998). While Kenny et al choose LAS which is associated with the brain-stem response and late cortical response to measure the DOA, Roy et al (1997), in their automatic feedback controlled propofol infusion system, use MLAEP (mid-latency auditory evoked potentials) which consists of the waves during 10-60ms of AER and is also known as early cortical response to derive the DOA through wavelet analysis and neural network training, Webb et al (1996) use the variations of Nb latencies in the early cortical response to assess the DOA.

Although AER is the best indicator of the transition from consciousness to unconsciousness, it does not correlate with the blood concentration of propofol during the emergence from

anaesthesia (Doi et al., 1997) and the patients have to wear headphones during surgery to receive the sound stimuli. Occasionally muscle responses will be evoked by the stimuli and cannot be removed by the computer averaging (Thornton and Newton, 1989). Nb wave was found to be able to characterize the transition from responsive to unresponsive, however it is not consistent with all patients (Stanski, 1994).

3.3.4.3.Bispectral Index

Clinicians administering anaesthetics and sedatives need to manage the hypnotic state of their patients, and patients undergoing surgery or intensive therapy require an adequate level of hypnosis to protect them from stress, awareness and recall of traumatic interventions. However, it is not currently possible to directly measure the hypnotic states. In clinical practice, an indirect assessment of hypnotic states is performed by observing physical signs and responsiveness to voice or touch at a lighter level of anaesthesia. Ideally, the hypnotic states should be assessed subjectively and automatically without introducing any stimulation. Potentially, this may provide better patient care. Bispectral Index or BIS, which describes the hypnotic states based on the bispectral analysis of EEG signal, has recently been developed by Aspect Medical Systems.

Bispectral analysis was initially used by Barnett et al (1971) and Dummermuth et al (1971) to study the EEG's inter-frequency coupling in a number of anaesthetic states including waking and sleeping. However, little progress was made due to the heavy computational requirements from this analysis. More recently, with the advent of high speed and low cost computing, the research of bispectral analysis on EEG signal has become active. Such research includes the evaluation of the non-linear relationships in the EEG from multiple recording sites (Saltzberg et al, 1986), the assessment of anaesthetic adequacy (Billard et al, 1994; Leslie et al, 1995; Liu, Singh and White, 1996).

While power spectral analysis suppresses the inter-frequency relationship, bispectral analysis measures the potential interactions between the wave components to determine whether dependent or harmonic components are present. As shown in Figure 3-18, the bispectrum quantifies the degree of phase coupling between every possible frequency pair combination and the frequency at their sum in order to determine if the component waves are harmonics or fundamentals.

The task of extracting clinically useful information from the bispectrum is to determine how changes in the bispectrum relates to changes in the EEG signal during the periods of altered

cerebral function, such as the administration of anaesthetics and neuroactive drugs. Visually, certain general patterns in the raw EEG signal have been recognised during anaesthesia when anaesthetic doses are increased. It has been noted that the EEG signal slows down and appears to become more synchronised. Power spectral analysis provides some identification of the "slow down" via increased delta frequency content. Bispectral analysis also trends these changes, but provides a measure of synchronisation via the degree of phase-coupling as well.

The Bispectral Index was generated from both power spectral analysis and bispectral analysis using a sophisticated proprietary algorithm. It is a composite, numerical index which tracks changes in the cerebral state and quantifies the overall bispectral properties (frequency, power and phase) throughout the entire frequency range (Table 2-1).

BIS is a real-time variable with values ranging from 0 to 100 showing hypnotic states or sedation levels. The bigger the value of the Bispectral Index, the lighter the depth of anaesthesia. Figure 3-19 shows a typical BIS trend in a volunteer study, in which the closed-loop controlled propofol infusion lasted 55 minutes.

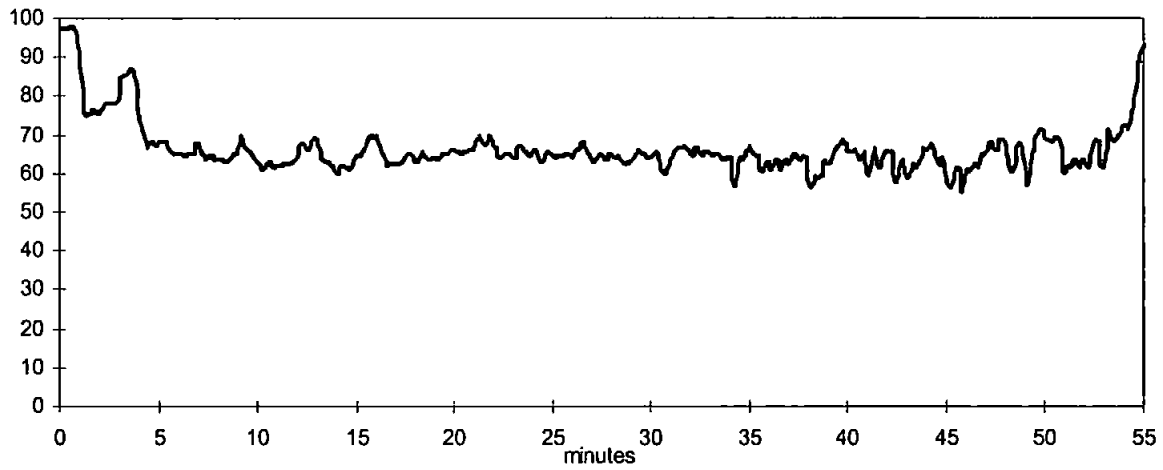


Figure 3-19 Typical BIS trend in a volunteer study

Before the calculation of BIS, the EEG segments with artefacts and suppressed EEG are identified and rejected, thereafter the index is calculated by combining the EEG features selected from a set of candidate bispectral and power spectral variables. The power spectral variables are used to extract the information hidden in the power of each sine wave component, while the bispectral variable is used to characterise the degree of phase coupling between the frequency components (Aspect Medical Systems, 1995).

The bispectral index has been prospectively validated with a large clinical database. Different versions of the bispectral index exist and data produced with one version of BIS are not necessarily compatible with those produced with another. The early versions of BIS were evaluated using prediction of movement to skin incision at the beginning of a surgical procedure. Although the early versions of BIS have demonstrated to be a good predictor of movement response to skin incision (Kearse et al., 1994a; Vernon et al., 1995) and hemodynamic response to intubation (Kearse et al., 1994b) for the specific drug regimens, it is not a good predictor of movement across some commonly used drug combinations that include the use of varying doses of opioids. The available version of BIS algorithm (version 3.12) at the time of this project provides a measure of the effects of anaesthetics and other pharmacological agents on the hypnotic state of the brain (Kearse et al., 1995; Liu, Singh and White, 1996; Pearson et al., 1996). It was reported that the BIS both correlated well with the level of responsiveness and provided an excellent prediction of the loss of consciousness (Glass et al., 1997), and that BIS is linearly correlated with the blood concentration of propofol (Leslie et al., 1995; Doi et al., 1997) and the magnitude of the cerebral metabolic reduction caused by propofol and isoflurane anaesthesia which suggests that a physiologic link exists between the EEG and cerebral metabolism during anaesthesia that is mathematically quantifiable (Alkire, 1998).

4. A Mathematical Model of Closed-loop Controlled Anaesthesia

4.1. Introduction

The development of the closed-loop anaesthesia (CLAN) control system includes system model development, test of the model, and the implementation of the physical system with hardware and software components. Modelling of the system before the design and implementation of the physical system has great advantage. A model provides an efficient way to investigate the closed-loop anaesthesia control with a wide range of control strategies. The problems associated with the closed-loop anaesthesia control (e.g. patient variability, drug interaction) can also be investigated with the model, which would significantly improve the reliability of the implemented system and patient safety.

4.1.1. Feedback Signals

For any closed-loop control system, a feedback signal that measures the desired effect of the control action is required. In a closed-loop anaesthesia system, the feedback signal is the depth of anaesthesia in patients. The choice of such feedback signal however is currently controversial due to the lack of a unifying definition for the depth of anaesthesia (Ogata, 1987). The anaesthetic state is a complex function of unconsciousness, amnesia, analgesia, motionlessness, and autonomic stability. Although it is not yet possible to quantify the complete anaesthetic state when numerous drugs are used in operating theatres, meaningful feedback signals are available for some components of the anaesthetic state (e.g., muscle relaxation, hemodynamics, sedation). Currently median frequency, auditory evoked response and Bispectral Index are the feedback signals used in closed-loop anaesthesia systems for sedation control.

In comparison with other commonly used DOA indicators, the Bispectral Index has the best correlation with the calculated blood propofol concentration (Doi et al., 1997), the best correlation with the magnitude of the cerebral metabolic reduction (Alkire, 1998) and is considered as the best indicator of DOA (Smith, Dutton and Smith, 1996). Therefore BIS is selected as the measure of depth of anaesthesia and therefore the feedback signal of the closed-loop anaesthesia system.

4.1.2. Control Strategy

The controlled object in closed-loop anaesthesia control is the depth of anaesthesia or DOA in patients. The complex and varying dose-effect relationship in individual patients during drug

infusion and the lack of a 'gold standard' in anaesthesia monitoring make the DOA control difficult.

As introduced in Chapter 2, the dynamics of drug disposition in the human body is quite complex after a certain amount of drug has been infused, and the mathematical modelling of those dynamics are far from perfect. Some factors affecting the dose-effect relationship, such as health condition and drug history of patients, are not modelled or unknown; these cause variability among patients and even within a single patient being anaesthetised. On the other hand, significant non-linearity exists in all existing anaesthetic depth descriptors though their trends could linearly correlates with the drug effect, such as Bispectral Index. The control signal is also non-linear due to the fact that it is impossible to take any infused drug out of a patient. Another problem in closed-loop anaesthesia control is the drug effect hysteresis that varies from one patient to another.

Since a closed-loop anaesthesia system could potentially be used with patients in the operating theatre during surgery, it is essential that such a system is able to respond quickly to any inadequate anaesthesia caused by stimulation while ensuring the safety of patients. A PID controller is therefore a good choice for its quick response and less computational complexity.

Target Controlled Infusion (TCI) has achieved significant success in clinical practice. Though TCI is an open-loop control scheme, the target drug concentration for individual patient is actually adjusted by an anaesthetist in practice, and this adjustment is based upon the depth of anaesthesia monitoring and the anaesthetist's experience. To take advantage of the TCI technology, a TCI component is to be used in the closed-loop anaesthesia system to drive directly an infusion pump, while the PID controller acts like the anaesthetist to adjust the target drug concentration of the TCI component.

One of the major advantages of using a TCI system in the closed-loop anaesthesia system is that patient safety could be further ensured when the closed-loop control system malfunctions or the feedback signal is not available or bad in quality. In these circumstances, the closed-loop control can be easily switched to open-loop TCI control, and switched back after the problem has been resolved.

Due to the existence of non-linearity and unknown dynamics in the closed-loop anaesthesia system, a system control unit is introduced to monitor and modify the behaviour of the PID controller and the infusion rate given by the TCI. This unit also contains digital signal processing and improves the level of confidence on patient safety in the use of closed-loop

anaesthesia system.

4.1.3. System Block Diagram

Based on the above discussions, the block diagram of the proposed closed-loop anaesthesia (CLAN) control system is shown in Figure 4-1.

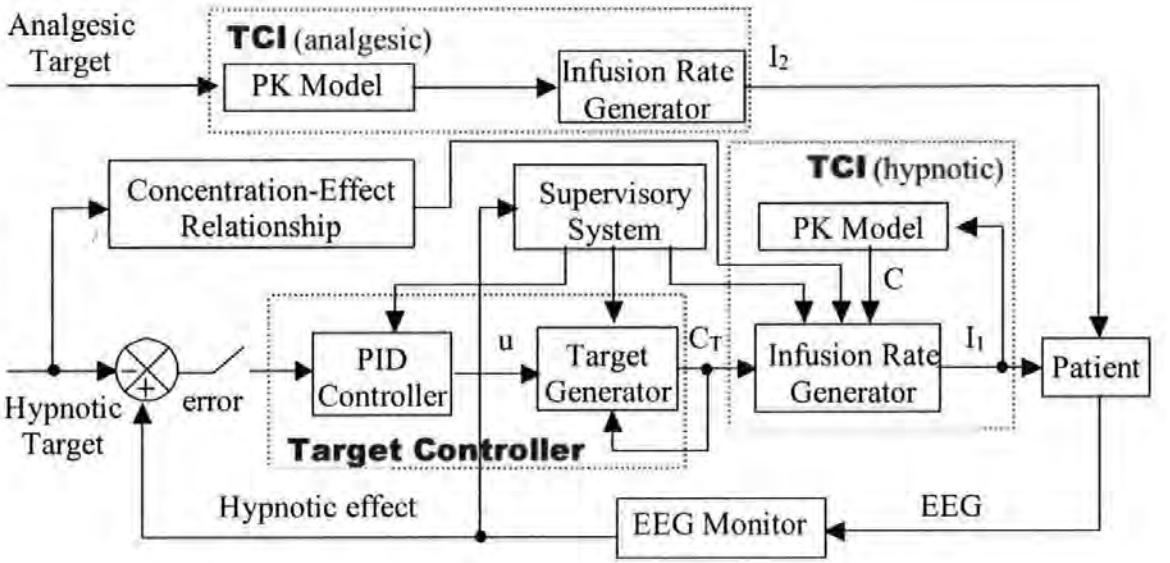


Figure 4-1 The Block diagram of the closed-loop anaesthesia system to be investigated and evaluated on human subjects

For the system shown in Figure 4-1, two drugs can be infused simultaneously to achieve total intravenous anaesthesia. One is an analgesic agent controlled by a dedicated TCI component through the open-loop path, and the other drug is a hypnotic agent controlled by a feedback system through the closed-loop path with incorporation of another TCI component. In the open-loop path, an anaesthetist adjusts manually the target analgesic concentration, whereas it is the target controller that adjusts automatically the target hypnotic concentration (C_T) of the associated TCI component in the closed-loop path. The TCI then generates a drug infusion rate (I_1) at which the drug is to be infused intravenously into patient. The closed-loop system starts the drug infusion with a bolus that is calculated by the TCI component from the DOA target using the relationship between drug concentration and drug effect. The supervision system is a central control and digital signal processing unit monitoring the quality of feedback signal, the error signal, the infusion rate generated, and the safety of patient. When the absence of quality feedback signal is persistent, for example, the supervision system would switch the closed-loop control to open-loop TCI control.

A mathematical model of the CLAN system shown in Figure 4-1 has been developed for the CLAN investigations on virtual patients. This model, as shown in Figure 4-2, consists of a pharmacokinetic model, a pharmacodynamic model which models the EEG monitor in the CLAN system, a patient model, a PID controller, a target generator, and an infusion rate generator.

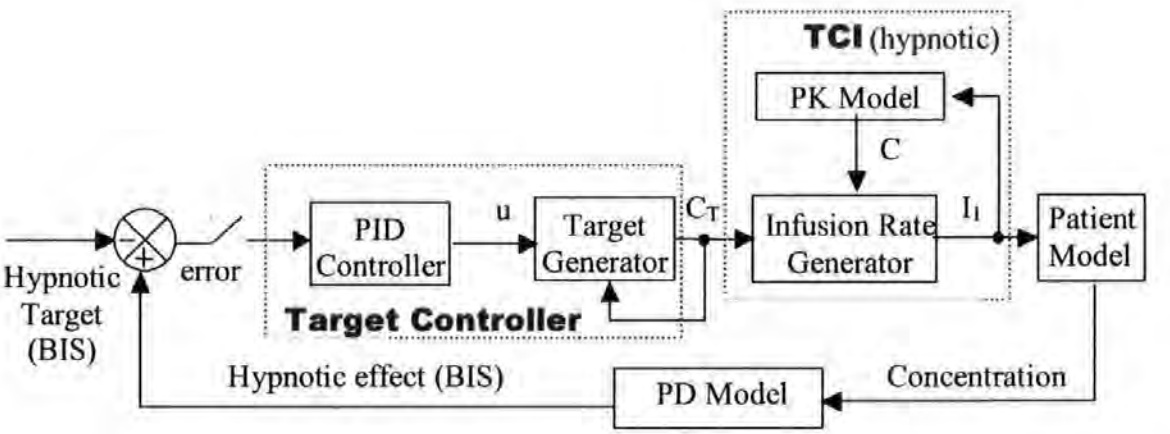


Figure 4-2 The mathematical model of the closed-loop path of the system shown in Figure 4-1

The PK model and PD model in Figure 4-2 are reference models with population average parameter values, while the patient model is an independent pharmacokinetic model with patient specific parameter values to be defined in Section 4.4.

4.2. Pharmacokinetic Model

As described in Chapter 2, pharmacokinetics characterizes the dose-concentration relationship following a bolus infusion, and a pharmacokinetic model is a mathematical representation of this relationship. The drug distribution process in human body could be described with a hydraulic-like multi-compartment model as shown in **Figure 2-3** and Figure 2-4. In this project, the three-compartment pharmacokinetic model with additional effect site compartment as shown in Figure 2-4 is adopted because it is widely used in clinical research for its simplicity with sufficient precision and computational efficiency. The mathematical representation of the pharmacokinetic model as shown in Figure 2-4 will be derived by constructing the dose-plasma concentration relationship and dose-effect site concentration relationship. For convenience, the pharmacokinetic model as shown in Figure 2-4 is reproduced in Figure 4-3.

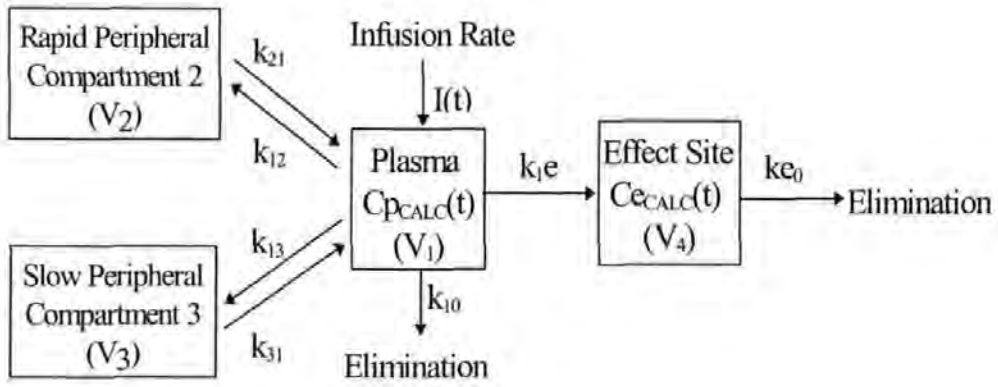


Figure 4-3 Three-compartment pharmacokinetic and one effect site compartment modelling for intravenous drug infusion

where k_{ij} is drug transfer rate between plasma and rapid/slow compartments, k_{e0} is elimination rate of drug from effect site to environment; k_{1e} is drug transfer rate from plasma to effect site; V_i is volume of individual compartment with V_4 negligible; $I(t)$ is drug infusion rate over time; $Cp_{CALC}(t)$ is predicted plasma concentration; $Ce_{CALC}(t)$ is predicted effect site concentration.

In Figure 4-3, the change of concentration in the central compartment at any time is related to the drug transferred to and from the peripheral compartments, and the drug eliminated from and infused into the central compartment at that time. Similarly, the change of concentration in a peripheral compartment is associated with the drug transferred to and from the central compartment at any time. Hence the pharmacokinetic model can be characterized by the following differential equations:

$$\frac{dC_1(t)}{dt} = -(k_{10} + k_{12} + k_{13})C_1(t) + k_{21}C_2(t) + k_{31}C_3(t) + \frac{I(t)}{V_1} \qquad (4\text{-}1)$$

$$\frac{dC_2(t)}{dt} = k_{12}C_1(t) - k_{21}C_2(t) \qquad (4\text{-}2)$$

$$\frac{dC_3(t)}{dt} = k_{13}C_1(t) - k_{31}C_3(t) \qquad (4\text{-}3)$$

where $C_1(t)$, $C_2(t)$, $C_3(t)$ are the drug concentrations ($ng \cdot ml^{-1}$) at time t in the central compartment, rapid and slow equilibration compartments, respectively.

By applying the Laplace transform, the differential equations become

$$sC_1(s) = -(k_{10} + k_{12} + k_{13})C_1(s) + k_{21}C_2(s) + k_{31}C_3(s) + V_1^{-1}I(s) \quad (4\text{-}4)$$

$$sC_2(s) = k_{12}C_1(s) - k_{21}C_2(s) \quad (4\text{-}5)$$

$$sC_3(s) = k_{13}C_1(s) - k_{31}C_3(s) \quad (4\text{-}6)$$

Solving for $C_1(s)$ and replacing it with $Cp_{CALC}(s)$, gives

$$Cp_{CALC}(s) = \frac{I(s)(b_2s^2 + b_1s + b_0)}{a_3s^3 + a_2s^2 + a_1s + a_0} \quad (4\text{-}7)$$

where

$$\begin{cases} a_0 = k_{10}k_{21}k_{31} \\ a_1 = k_{10}k_{21} + k_{10}k_{31} + k_{12}k_{31} + k_{13}k_{21} + k_{31}k_{21} \\ a_2 = k_{10} + k_{12} + k_{21} + k_{13} + k_{31} \\ a_3 = 1 \\ b_0 = k_{21}k_{31}V_1^{-1} \\ b_1 = k_{21} + k_{31}V_1^{-1} \\ b_2 = V_1^{-1} \end{cases} \quad (4\text{-}8)$$

Applying Laplace transform on (2-2)

$$Cp_{CALC}(s) = I(s)D_p(s) \quad (4\text{-}9)$$

where $D_p(s)$ is the Laplace transformation of $D_p(t)$ or the transfer function of the drug disposition dynamic system. Solving equations (4-7) and (4-9) for $D_p(s)$:

$$D_p(s) == \frac{(b_2s^2 + b_1s + b_0)}{a_3s^3 + a_2s^2 + a_1s + a_0} \quad (4\text{-}10)$$

Suppose α, β, and γ are the roots of the characteristic equation (polynomial denominator) in (4-10), then $D_p(s)$ can be rewritten as:

$$D_p(s) = \frac{(b_2s^2 + b_1s + b_0)}{(s+\alpha)(s+\beta)(s+\gamma)} \quad (4\text{-}11)$$

or

$$D_p(s) = \frac{A_1}{s+\alpha} + \frac{A_2}{s+\beta} + \frac{A_3}{s+\gamma} \tag{4-12}$$

where A_1, A_2, and A_3 can be solved from equation (4-11) and (4-12)

$$\begin{cases} A_1 = \dfrac{b_2\alpha^2 - b_1\alpha + b_0}{(\beta-\alpha)(\gamma-\alpha)} \\ A_2 = \dfrac{b_2\beta^2 - b_1\beta + b_0}{(\alpha-\beta)(\gamma-\beta)} \\ A_3 = \dfrac{b_2\gamma^2 - b_1\gamma + b_0}{(\alpha-\gamma)(\beta-\gamma)} \end{cases} \tag{4-13}$$

The drug disposition function $D_p(t)$ as presented in equation (2-3) can be obtained by taking reverse Laplace transform on Equation (4-12):

$$D_p(t) = A_1 e^{-\alpha t} + A_2 e^{-\beta t} + A_3 e^{-\gamma t} \tag{4-14}$$

On the contrary, the volume in central compartment (V_1) and rate constants in a compartment model can be derived from the parameters of the corresponding mathematical model (i.e., A_1, A_2, A_3 and α, β, γ).

Rewrite (4-11) as following

$$D_p(s) == \frac{d_2s^2 + d_1s + d_0}{c_3s^3 + c_2s^2 + c_1s + c_0} \tag{4-15}$$

where

$$\begin{cases} c_0 = \alpha\beta\gamma \\ c_1 = \alpha\beta + \beta\gamma + \gamma\alpha \\ c_2 = \alpha + \beta + \gamma \\ c_3 = 1 \\ d_0 = A_1\beta\gamma + A_2\gamma\alpha + A_3\alpha\beta \\ d_1 = A_1(\beta+\gamma) + A_2(\gamma+\alpha) + A_3(\alpha+\beta) \\ d_2 = A_1 + A_2 + A_3 \end{cases} \tag{4-16}$$

Equations (4-10) and (4-15) should be identical, therefore for (4-8) and (4-16), the followings are true

$$\begin{cases} a_i = c_i & i = 0,1,2,3 \\ b_j = d_j & j = 0,1,2 \end{cases} \tag{4-17}$$

Finally, the central compartment volume V_1 and the rate constants (k_{10}, k_{12}, k_{13}, k_{21}, k_{31}) can be solved from equation (4-17).

Now, the dose-concentration relationship in plasma has been constructed. However, to model the dose-concentration relationship at the effect site, the relationship between the plasma concentration and the concentration at the site of drug action needs to be built.

To calculate the effect site drug concentration, another differential equation is identified:

$$\frac{dC_{eCALC}(t)}{dt} = k_{1e}C_{pCALC}(t) - k_{e0}C_{eCALC}(t) \tag{4-18}$$

Applying Laplace transform to equation (4-18):

$$sC_{eCALC}(s) = k_{1e}C_{pCALC}(s) - k_{e0}C_{eCALC}(s) \tag{4-19}$$

Considering that k_{1e} and k_{e0} are equal in value because of the negligible volume of the effect site compartment, then

$$C_{eCALC}(s) = \frac{k_{e0}}{s + k_{e0}} C_{pCALC}(s) \tag{4-20}$$

or

$$D_e(s) = \frac{C_{eCALC}(s)}{C_{pCALC}(s)} = \frac{k_{e0}}{s + k_{e0}} \tag{4-21}$$

where $D_e(s)$ is the transfer function. From equations (4-20) and (4-21), the drug disposition function from plasma to the effect site ($D_e(t)$) and the effect site drug concentration ($C_{eCALC}(t)$) can be described by the following equations.

$$D_e(t) = k_{e0}e^{-k_{e0}t} \tag{4-22}$$

$$C_{eCALC}(t) = \int_0 D_e(t-\tau)C_{pCALC}(\tau)d\tau \tag{4-23}$$

This drug transfer process can be represented by a dynamic system shown in Figure 4-4.

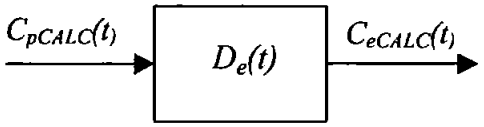


Figure 4-4 Drug disposition dynamic system of effect site

The complete dose-effect site concentration relationship can then be obtained by combining equation (4-10) and (4-21), and described by the following system:

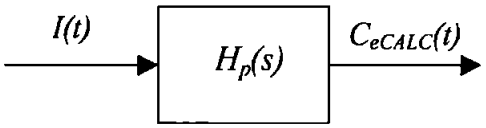


Figure 4-5 Drug disposition dynamic system (dose-concentration relationship)

where $I(t)$ is the infusion rate over time, $C_{eCALC}(t)$ is the effect site drug concentration over time, and $H_p(s)$ is the transfer function of this dynamic system in Laplace domain defined by the following expression:

$$H_p(s) = D_p(s) \times D_e(s) = \frac{k_{e0}(b_2 s^2 + b_1 s + b_0)}{(a_3 s^3 + a_2 s^2 + a_1 s + a_0)(s + k_{e0})} \qquad (4\text{-}24)$$

So far, the effect site concentration can be estimated from the dose of the drug infused, and (4-10) and (4-24) define the generic mathematical expression of the transfer function of drug disposition in plasma and effect site. Different sets of parameters are associated with different patients. A TCI module of the closed-loop anaesthesia system uses a set of population average parameters, whereas the patient models to be presented later use a wide range of parameter sets in the investigations.

4.3. Pharmacodynamic Model

Pharmacodynamics characterizes the relationship between drug concentration at site of action

and the intensity of biological effect, (i.e., the concentration-effect relationship). This relationship, in pharmacology, is described by a sigmoid model (Holford and Sheiner, 1981) shown in Figure 2-5, and the mathematical expression of this relationship is presented in (2-4). However, if a descriptor, like Bispectral Index, represents a deeper anaesthetic depth with a smaller value, the corresponding sigmoid model and its mathematical expression are different from those presented previously. These are shown in Figure 4-6 and equation (4-25).

$$E = E_0 \cdot (1 - \frac{C^{\gamma}}{C_0^{\gamma} + C^{\gamma}}) - E_{max} \qquad (4\text{-}25)$$

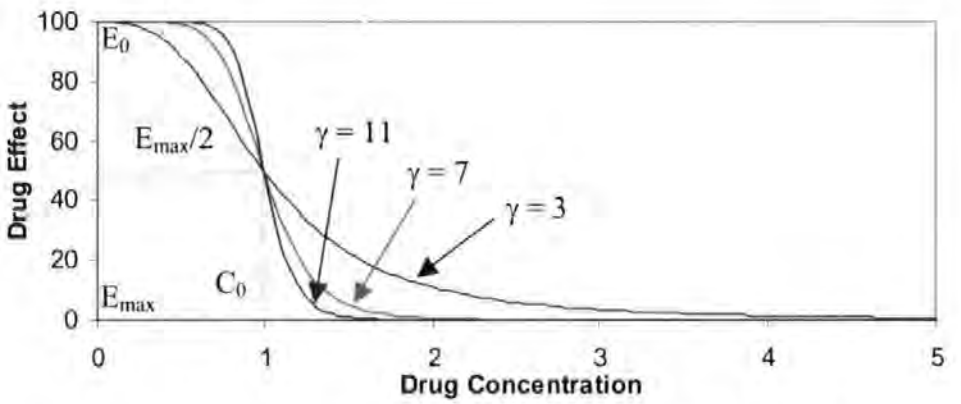


Figure 4-6 Pharmacodynamic sigmoid model for drug effect descriptors like Bispectral Index (E_0 : baseline effect, E_{max} : max effect, C_0 : drug concentration to achieve 50% of effect)

The pharmacodynamic sigmoid model represented by equation (4-25) generally defines the shape of the sigmoid curve. However, different patients may have their own models characterized by a set of pharmacodynamic parameters (i.e., E_0, E_{max}, C_0, and γ). Figure 4-6 shows three versions of the model with varying γ values (γ=3, 7, 11).

The sigmoid model is mathematically complex, especially when γ is not an integer. However the dose-effect relationship for some drugs might be roughly linear, for example, dose-BIS effect (Doi et al., 1997; Leslie et al., 1995), in which case a linear approximation of the sigmoid model could exist and has the following forms depending upon the definition of the anaesthetic depth descriptor.

$$E = k \times C \qquad (4\text{-}26)$$

or if smaller descriptor value represents a deeper depth of anaesthesia

$$E = -k \times C + b \tag{4-27}$$

where k is the slope of the relationship line, and b is the baseline value of the drug effect. Doi et al (1997) derived, by linear regression on the data obtained from a group of patients, a simple linear relationship equation for concentration-BIS effect in their clinical study. This relationship is shown in equation (4-28).

$$BIS(k) = -12.837 \times C(k) + 93.582 \tag{4-28}$$

$$BIS(z) = -12.837C(z) + \frac{93.582z}{z-1} \tag{4-29}$$

where *BIS* is the Bispectral Index, and C is the steady state drug concentration in plasma. Steady state is a state in which the drug concentrations in plasma and at effect site equilibrate, and this meets the requirement of the concentration-effect relationship. The pharmacodynamic sigmoid model for BIS effect for patients who have concentration-effect relationship described by the equation (4-28) can be reconstructed and is shown in Figure 4-7 where the thick line is the approximation of the sigmoid curve.

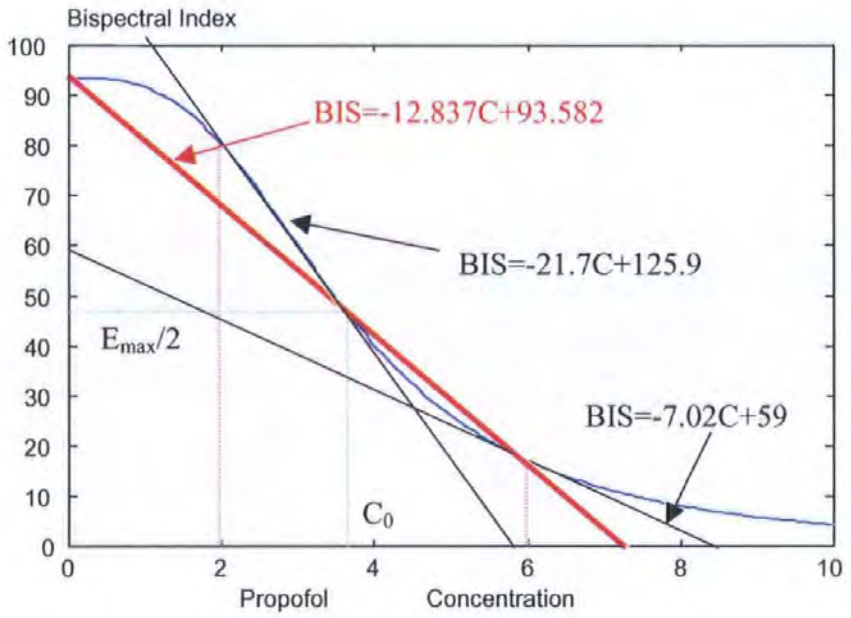


Figure 4-7 Pharmacodynamic sigmoid models for BIS-Propofol concentration relationship

In Figure 4-7, the y axis is drug effect or Bispectral Index (BIS), the x axis is steady state or effect site drug concentration (C), BIS_0 is baseline BIS effect (BIS_0=93.582), BIS_{max} is

maximum BIS effect (BIS_{max}=0), C_0 is effect site drug concentration when 50% of drug effect has been achieved, and γ is the steepness of the relationship curve (γ=3 in this case).

The pharmacodynamic model represented by equation (4-28) is used for the test of pharmacokinetic variability in patients, whereas other two pharmacodynamic models are to be used as variations for the test of pharmacodynamic variability in patients. These two models have the following mathematical representations as shown in Figure 4-7.

$$BIS(k) = -21.7.C(k) + 125.9 \qquad (1.2 \le C \le 5.8) \qquad (4\text{-}30)$$

$$BIS(k) = -7.02.C(k) + 59 \qquad (0 \le C \le 8.4) \qquad (4\text{-}31)$$

For above two arbitrarily selected pharmacodynamic models, the BIS-Concentration relationship is only valid within the specified range of drug concentration. The reason to choose these two linear models is based upon the fact that, for most patients in general anaesthesia, the propofol drug concentration would likely fall within 2~6 mcg/ml for the majority period of drug administration time, and the linear models shown in equation (4-30) and (4-31) approximately represent the BIS-Concentration relationship when propofol drug concentration C is 2~4 mcg/ml or around 6 mcg/ml. The slopes of the two linear models may change when the steepness of the sigmoid curve (γ) varies.

4.4. Patient Model

Now it is clear that the drug distribution of a patient can be described by a set of pharmacokinetic/dynamic parameters, that is to say that a patient could be modelled by specifying these parameters. However, it is not known which pharmacokinetic/dynamic parameter sets are the extremes in the whole population of patients, with which the patients need the most or least drug to achieve a certain level of anaesthesia than the others.

To investigate patient variability, the pharmacokinetic parameters obtained by Gepts et al (1987) and the pharmacodynamic parameters by Doi et al (1997) are used to model the patients for testing the mathematical model and the closed-loop anaesthesia system to be developed. The pharmacokinetic parameters are summarised in Table 4-1. The table also gives the upper and lower 95% confidence interval (CI) calculated from the mean and the standard deviation. The data from Table 4-1 are used to model a range of hypothetical patients and the TCI component of the closed-loop anaesthesia system.

Table 4-1 Mean, standard deviation (SD) and 95% confidence intervals (CI) of pharmacokinetic rate constants and central compartment volume, Gepts et al (1987)

	Mean	**SD**	**Upper 95% CI**	**Lower 95% CI**
$k_{10}(min^{-1})$	0.119	0.0688	0.1357	0.1023
$k_{12}(min^{-1})$	0.114	0.206	0.164	0.064
$k_{13}(min^{-1})$	0.0419	0.0304	0.0493	0.0345
$k_{21}(min^{-1})$	0.055	0.1094	0.0815	0.0285
$k_{31}(min^{-1})$	0.0033	0.0025	0.0039	0.0027
V_1(litre)	16.924	6.957	20.2	13.6

The drug transfer rate constant ke_0 is usually calculated from patient's weight and the drug effect peak time. The range of 1-2.4 minutes for propofol was reported from the latest research (Schnider et al., 1999) on the peak time of drug effect, therefore the peak time values of 1 minute and 2.4 minutes are used together with their mean value (1.7 minutes) for the patient models. For pharmacodynamic models of patients, the linear regression model presented in (4-28) is used as the population average model along with the linear models presented in (4-30) and (4-31).

The drug effect peak times and the linear pharmacodynamic model parameters are summarized in Table 4-2.

Table 4-2 Drug effect peak time and pharmacodynamic model parameters

	average	**high**	**low**
t_p (min)	1.7	2.4	1
k	-12.837	-21.7	-7.02
b	93.582	125.9	59

In the closed-loop anaesthesia system shown in Figure 4-1, a pharmacokinetic model is built

into the TCI component for hypnotic propofol infusion. This PK model acts as a standard *reference model* to estimate the drug concentration in patients, and a population average PK model, which is the mean value listed in Table 4-1 and listed separately in Table 4-3, is adopted for this purpose. The peak time (t_p) of drug effect shown in Table 4-3 is the mean value obtained by Schnider et al (1999).

Table 4-3 Population average pharmacokinetic model parameters of the TCI component for propofol infusion in closed-loop anaesthesia system

$k_{10}(min^{-1})$	$k_{12}(min^{-1})$	$k_{13}(min^{-1})$	$k_{21}(min^{-1})$	$k_{31}(min^{-1})$	$V_1(litre)$	$t_p(min)$
0.119	0.114	0.0419	0.055	0.0033	16.9	1.7

For analgesic alfentanil infusion driven by another TCI component shown in Figure 4-1, the population average PK model in patients shown in Table 2-5 is used. The pharmacokinetic parameters of this model are reproduced in Table 4-4.

Table 4-4 Population average pharmacokinetic parameters of the TCI component for alfentanil infusion in closed-loop anaesthesia system

PK Parameters		**Value or Expressions**
K_{10}	**Age > 40yr**	$(0.356 - (0.00269 \,.\, (Age - 40))) / V_1$
(min^{-1})	**Age≤40yr**	$0.356/V_1$
$K_{12}\,(min^{-1})$		0.104
$K_{21}\,(min^{-1})$		0.0673
$K_{13}\,(min^{-1})$		0.017
K_{31}	**Age > 40yr**	$0.0126 - (0.000113 \,.\, (Age - 40))$
(min^{-1})	**Age≤40yr**	0.0126
V_1	**Men**	0.111 . Weight (in kg)
(litre)	**Women**	0.111 . 1.15 . Weight (in kg)
t_p (min)		1.376

In both Table 4-3 and Table 4-4, drug effect peak time t_p is used together with patient's weight for the calculation of k_{e0}, the elimination rate of drug from effect site to environment.

Because alfentanil infusion is entirely controlled by TCI in open-loop due to lack of real time measure of drug effect, no other patient models are developed.

For the investigation of closed-loop anaesthesia with pharmacokinetic variability on propofol infusion, 9 hypothetical patients (Patient1~Patient9) are modelled by using the data from Table 4-1 and Table 4-2. The 9 hypothetical patients, shown in Table 4-5, are obtained from the combination of upper 95% CI, lower 95% CI, and the peak times. Patient1~3 have the mean pharmacokinetic rate constants but different peak times, Patient4~6 have the rate constants with the values of the lower 95% CI and are associated with the same range of peak times, while the rate constants of Patients7~9 take the values of the upper 95% CI. Under the linear assumption of the drug distribution process, Patients1~9 would roughly represent the population studied by Gepts et al (1987). The parameters k and b are pharmacodynamic properties of the 9 patients. They are assumed to be constants with population average values for the investigation on pharmacokinetic variability.

Table 4-5 PK/PD parameter set of hypothetical patients with pharmacokinetic variability

Parameters	Patient1	Patient2	Patient3	Patient4	Patient5	Patient6	Patient7	Patient8	Patient9
$k_{10}(min^{-1})$	0.119			0.1023			0.1357		
$k_{12}(min^{-1})$	0.114			0.064			0.164		
$k_{13}(min^{-1})$	0.0419			0.0345			0.0493		
$k_{21}(min^{-1})$	0.055			0.0285			0.0815		
$k_{31}(min^{-1})$	0.0033			0.0027			0.0039		
V_1(litre)	16.9								
t_p (min)	1.7	2.4	1.0	1.7	2.4	1.0	1.7	2.4	1.0
k	-12.837								
b	93.582								

It is worth noting that the pharmacokinetic parameters of Patient1 are the same as those in the TCI reference model, and this patient is therefore a reference patient to demonstrate the biased drug concentration responses from other patients. From the pharmacokinetic parameter values listed in Table 4-5, it is confirmed that the largest overshoot would occur in Patient6 due to

the smallest clearance rates (k_{10}, k_{12}, and k_{13}) and shortest drug effect peak time (t_p), and on the contrary the largest undershoot will be in Patient8 who has the largest values in clearance rates and peak time.

The hypothetical patients listed in Table 4-5 are used for the investigation of effect from pharmacokinetic variability on drug infusion. To investigate the characteristics of pharmacodynamic variability in intravenous drug infusion, another group of virtual patients (Patient10~Patient18) are constructed using Patient1, Patient6, and Patient8 together with varying pharmacodynamic model parameters listed in Table 4-2. This group of virtual patients is listed in Table 4-6.

Table 4-6 PK/PD parameter set of hypothetical patients with pharmacodynamic variability

Parameters	Patient10	Patient11	Patient12	Patient13	Patient14	Patient15	Patient16	Patient17	Patient18
$k_{10}(min^{-1})$	0.119			0.1023			0.1357		
$k_{12}(min^{-1})$	0.114			0.064			0.164		
$k_{13}(min^{-1})$	0.0419			0.0345			0.0493		
$k_{21}(min^{-1})$	0.055			0.0285			0.0815		
$k_{31}(min^{-1})$	0.0033			0.0027			0.0039		
V_1(litre)	16.9								
t_{peak} (min)	1.7			1.0			2.4		
k	-12.837	-21.7	-7.02	-12.837	-21.7	-7.02	-12.837	-21.7	-7.02
b	93.582	125.9	59	93.582	125.9	59	93.582	125.9	59

Tto test the robustness of the closed-loop anaesthesia system, an extensive set of 78125 hypothetical patients is modelled with the PK/PD parameters shown in Table 4-7.

Table 4-7 Pharmacokinetic parameters used to model 78125 hypothetical patients

$k_{10}(min^{-1})$	$k_{12}(min^{-1})$	$k_{13}(min^{-1})$	$k_{21}(min^{-1})$	$k_{31}(min^{-1})$	t_{peak}(min)	V_1(litre)
0.1023	0.064	0.0345	0.0285	0.0027	1	13.6
0.11065	0.089	0.0382	0.04175	0.003	1.35	15.3

0.119	0.114	0.0419	0.055	0.0033	1.7	16.9
0.12735	0.139	0.0456	0.06825	0.0036	2.05	18.5
0.1357	0.164	0.0493	0.0815	0.0039	2.4	20.2

The rate constants and the central compartment volumes (V_1) in Table 4-7 are obtained by interpolating the data listed in Table 4-1. The peak time values are interpolation values from the peak time range listed in Table 4-2. Suppose to take randomly one entry from each column in Table 4-7, there are 5^7 or 78125 permutations in total, and each of these permutations can be used to model a virtual patient. The robustness test of the closed-loop anaesthesia system is only on pharmacokinetic variability to reduce the number of hypothetical patients, and all these patients have the population average pharmacodynamic characteristics (see Table 4-5).

4.5. *Target Controller*

The target controller consists of a PID controller and a target generator as shown in Figure 4-1. As introduced in Chapter 3, PID control is a simple and fast response control scheme in which the control signal consists of three terms namely proportional, integral, and derivative terms. The PID control law and its z-domain discrete transfer function are described in equations (3-16) and (3-20), and are reproduced in equations (4-32) and (4-33).

$$u(k) = K_p e(k) + K_i \sum_{n=1}^{k} \frac{T}{2}[e(n-1) + e(n)] + K_d \frac{e(k) - e(k-1)}{T} \qquad (4\text{-}32)$$

$$H_c(z) = K_p + K_i \frac{T}{2} \frac{1+z^{-1}}{1-z^{-1}} + K_d \frac{1-z^{-1}}{T} \qquad (4\text{-}33)$$

where $u(k)$ and $e(k)$ are control signal and error signal at time $t=kT$, $H_c(z)$ is the z-domain transfer function of the PID controller, T is the sampling period (see Section 6.2), and K_p, K_i and K_d are the gains of the controller which are designed in Section 6.6.

The PID controller modifies the target concentration of the TCI system in the target generator in the following way

$$C_T(k) = C_T(k-1) + u(k) \qquad (4\text{-}34)$$

The pulse transfer function is

$$H_T(z) = \frac{C_T(z)}{u(z)} = \frac{1}{1 - z^{-1}} \tag{4-35}$$

If the measured BIS value is below the target BIS previously set, which indicates a deeper than desired anaesthesia, a negative control signal u(k) would be generated, and this would decrease the target propofol concentration for the TCI, otherwise a higher target concentration is to be generated to produce a deeper anaesthesia.

4.6. Infusion Rate Generator

The infusion rate generator within a TCI component gives the drug infusion rate to the two anaesthesia pumps for either a hypnotic agent or an analgesic agent. The infusion rate can be easily solved from equation (4-9) if plasma is the site of target, and from Figure 4-5 and equation (4-24) the infusion rate can be obtained when effect site is the site of target. The solutions are presented in (4-36) and (4-37).

Infusion rate when targeting on plasma:

$$I(s) = \frac{Cp_{CALC}(s)}{D_p(s)} \tag{4-36}$$

Infusion rate when targeting on effect site:

$$I(s) = \frac{C_{eCALC}(s)}{H_p(s)} \tag{4-37}$$

4.7. Discussion and Conclusion

The development of the mathematical model assumes linear dose-concentration and linear dose-effect relationships. However, those relationships may vary in patients or even within a single patient during the course of drug infusion. This patient variability is now technically not quantifiable, and therefore the mathematical model is developed as a population average model. In clinical practice, this patient variability would bring uncertainty on the control of anaesthesia.

The limitation of the developed mathematical model comes from pharmacokinetics and pharmacodynamics, where some of the factors that affect the drug disposition are not modelled (such as age, sex, and health condition), and the linear approximation of patient specific sigmoid model introduces modelling error.

Though Bispectral Index has been evaluated as the best descriptor of anaesthetic depth, it lacks quantitative precision. The value of BIS under a specific depth of anaesthesia varies in patients, and BIS itself measured in a patient may be oscillatory over time even when drug is infused at a fixed maintenance rate.

In summary, a mathematical model of a closed-loop anaesthesia system has been developed. This model models all the components within the proposed CLAN system including the reference pharmacokinetic/pharmacodynamic model with population average parameters, patient models with patient specific parameters, target controller and infusion rate generator.

The mathematical model is developed in a way that allows replacement of any component models in anticipation of any progress in understanding the pharmacokinetics and pharmacodynamics in the future, and it provides a useful tool for further investigation on closed-loop anaesthesia control.

5. Investigation of Closed-loop Anaesthesia

5.1. Introduction

Taking advantage of the mathematical model of closed-loop anaesthesia system, the following sections are to investigate closed-loop anaesthesia and identify the major problems existing in an intravenous drug delivery system. All investigations are based upon the mathematical model of the closed-loop path in the system shown in Figure 4-1.

As can be seen in Figure 4-1, the drug infusion is directly controlled by the TCI component of the CLAN system based upon a target drug concentration given by the target controller. Two sites are usually used as the sites of target: plasma and effect site. Targeting on plasma results in a slow growing of drug concentration without overshoot. However, it takes a significantly longer time to achieve the desired drug effect. On the other hand, targeting on effect site anticipates the drug distribution loss before the desired drug effect has been achieved, and hence additional drug is to be infused to compensate the distribution loss of drug. This results in overshoot in drug concentration but less time is taken to achieve the desired drug effect. In this Chapter, a control scheme in which the target site is switched between plasma and effect site is investigated.

This investigation also explores the nature of pharmacokinetic and pharmacodynamic variability in patients and how this variability affects the drug delivery by using 18 hypothetical patients listed in Table 4-5 and Table 4-6. Finally, the mathematical model is used for the investigation of closed-loop anaesthesia with the same patients. This investigation demonstrates how the CLAN model solves the problem of patient variability.

Unless explicitly stated otherwise, a target Bispectral Index of 65 is applied to achieve light anaesthesia (Baker, Sleigh and Smith, 2000), whereas an equivalent target drug concentration of 2.2265 mcg/ml is used when only a TCI model is required. The target concentration is derived from the Bispectral Index target using the BIS-concentration relationship presented in Section 4.3.

5.2. Targeting on Plasma or Effect Site Drug Concentration

When TCI is used to target on plasma, the target drug concentration would be achieved in plasma immediately after a bolus infusion as drug concentration peaks almost instantaneously in plasma. However, if effect site is the target site, there will be a delay or hysteresis for the effect site drug concentration to reach the target concentration, and this delay varies from one

patient to another.

Due to the delay of drug transfer from plasma to effect site, part of the bolus will be lost during the drug distribution, and look-ahead compensation for the drug distribution loss is therefore needed. In effect site target control mode, this compensation is incorporated into the initial bolus.

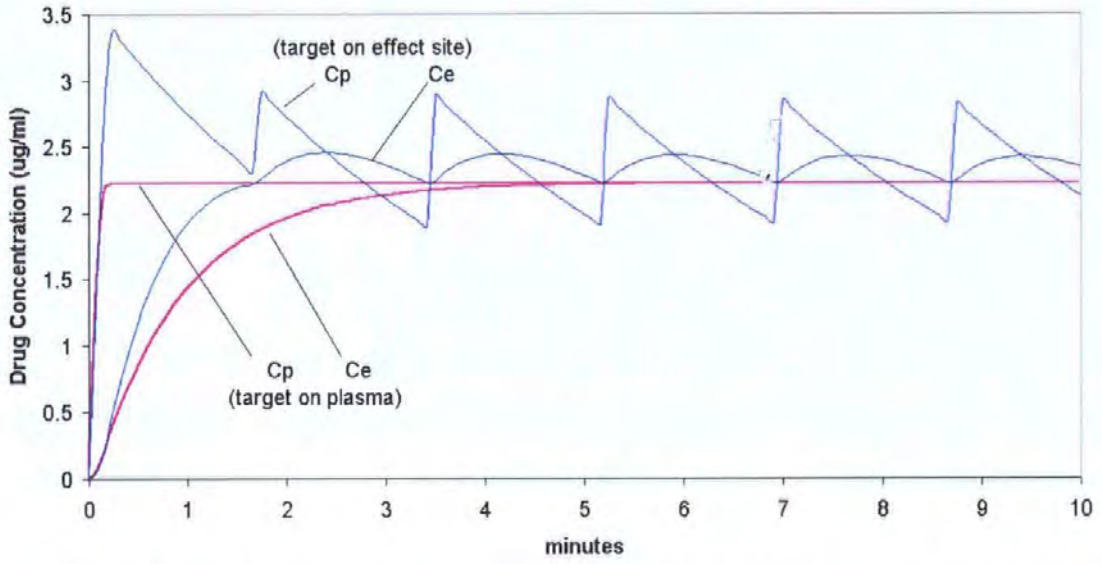


Figure 5-1 Predicted drug concentration in plasma (Cp) and effect site (Ce) in a patient with average PK paramters in two TCI control modes

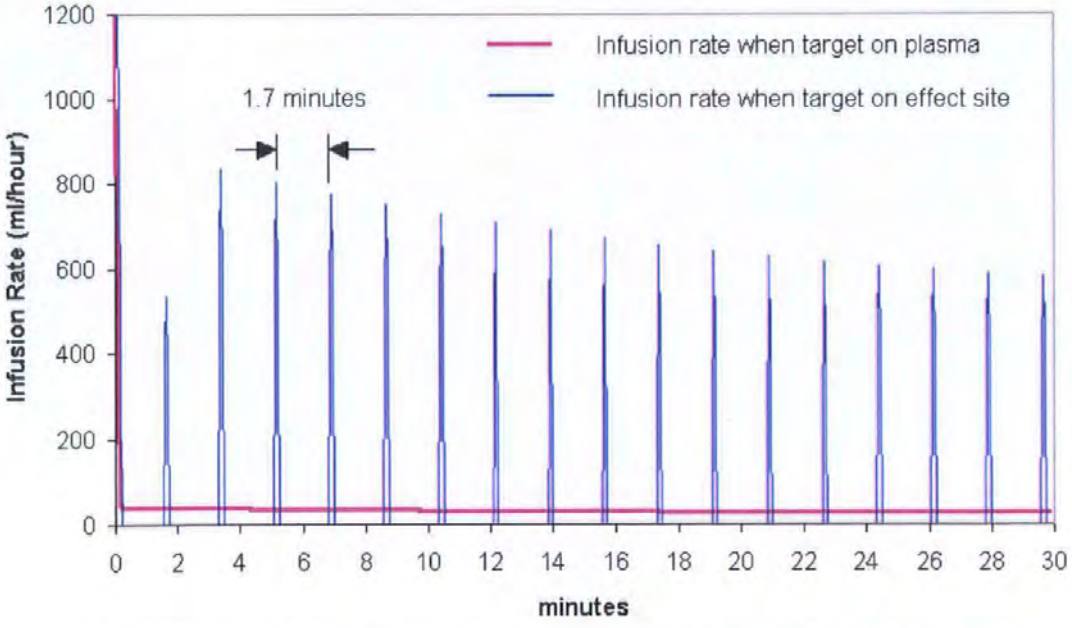


Figure 5-2 Infusion rate of a patient with average PK paramters in the two control schemes

Presented in Figure 5-1 and Figure 5-2 are the results from the computer simulations of the developed TCI model implemented in MATLAB. Figure 5-1 shows the predicted plasma drug concentration (Cp) and effect site drug concentration (Ce) over time when targeting either in plasma or effect site, while Figure 5-2 shows the drug infusion rate generated by the reference model from two control modes.

The reason why there is no overshoot in maintenance phase when targeting on plasma is because the infusion rate is significantly low and the drug infusion is continuous (see Figure 5-2). With the low rate and continuous infusion, the compensation for the drug distribution loss is only for 5 seconds rather than 1.7 minutes as is the case when targeting on effect site. This small compensation is not big enough to cause the overshoot.

Although targeting on plasma can achieve the target plasma concentration almost instantly and maintains the target smoothly, effect site is the site of drug effect and represents the level of anaesthesia. When targeting on plasma, it takes about 4.5 minutes for the effect site concentration to reach the target concentration, whereas 1.7 minutes is needed if effect site is the target site. In maintenance phase, effect site targeting causes overshoot in drug concentration periodically due to the look-ahead compensation, the infusion rate is intermittent and high, while plasma targeting maintains a stable effect site concentration with a steady, continuous, and much lower infusion rate.

5.3. Targeting on Mixed Sites

By combining the advantages of both TCI infusion schemes, the slow effect site concentration response in induction phase presented by plasma targeting and the periodical overshoot in maintenance phase caused by effect site targeting can be solved. Figure 5-3 and Figure 5-4 present the result from the mixed site target control strategy, where effect site target control is used for the induction and plasma target control for the maintenance. In this target control strategy, the initial bolus is calculated using effect site as the target site. When predicted effect site concentration peaks and reaches the target concentration (at 1.7 minute), the target site is switched to plasma.

There is no drug infusion after the initial bolus until the target site is changed into plasma (see Figure 5-4). Thereafter the drug was infused with a low maintenance rate calculated by the reference model that aims at compensating the drug distribution loss in the body of patient.

The maintenance infusion rate becomes lower and lower because the loss of drug in a patient is getting smaller and smaller according to the mathematical model of this process.

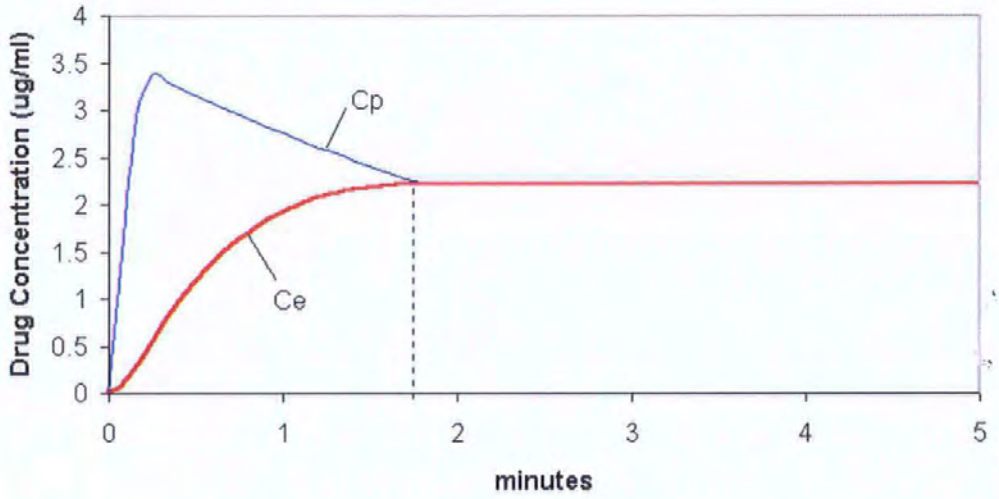


Figure 5-3 Plasma and effect site drug concentration when targeting on mixed sites (Cp: plasma drug concentration, Ce: effect site drug concentration)

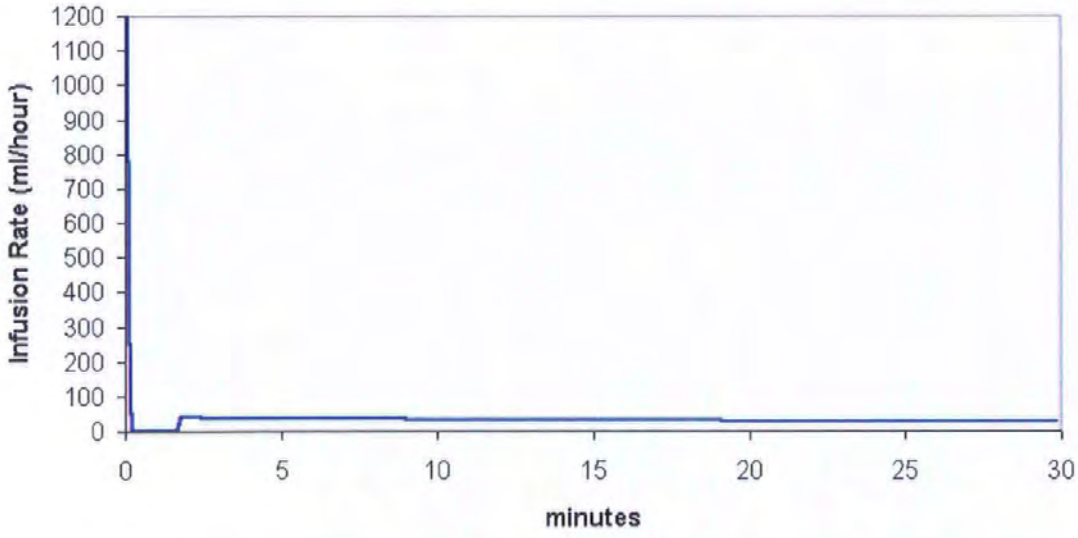


Figure 5-4 Drug infusion rate generated by the mixed site target control scheme

5.4. *Exploring Patient Variability*

According to clinical observations, inter-individual variability exists in human patients in pharmacokinetics and pharmacodynamics during drug administration. To investigate how this patient variability behaves when the hypnotic agent propofol is given, the pharmacokinetic model (TCI) and pharmacodynamic model (BIS-Concentration relationship) developed in Chapter 4 are used together with the 18 virtual patients modelled in Table 4-5 and Table 4-6. Both models are implemented in MATLAB and run on each of the 18 virtual patients in turn. The mixed site target control scheme is used for the following investigation of inter-individual variability in patients.

One of the basic assumptions implied in the previous investigations in sections 5.2 and 5.3 is that the patient's pharmacokinetic/pharmacodynamic characteristics are the same as described by the population average reference models. In reality, this is not true because of patient variability. Due to the identical reference model, the same initial bolus and maintenance infusion rate shown in Figure 5-4 are generated by the system for virtual patients Patient1~Patient18 intending to achieve and maintain drug concentration of 2.2265 mcg/ml at effect site. However, the TCI system fails to do so on most of these virtual patients. The result of the investigation on pharmacokinetic variability is shown in Figure 5-5, Figure 5-6, and Figure 5-7, where plasma and effect site drug concentration in Patient1~Patient9 are marked, and the infusion rate over time for the patients is the same as shown in Figure 5-4.

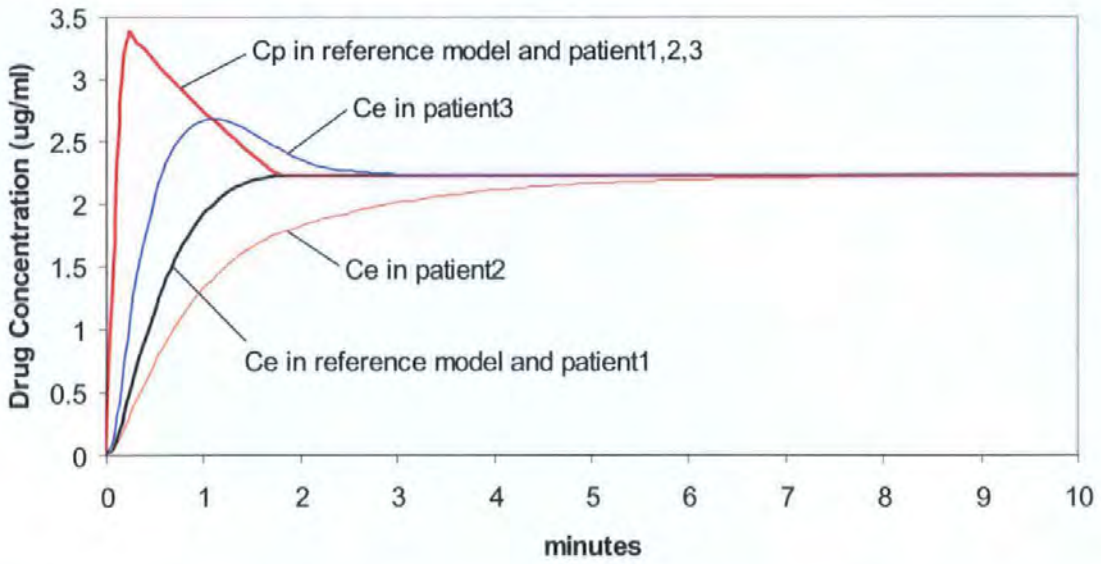


Figure 5-5 Drug concentrations of patient1, 2, and 3 in comparison with those predicted

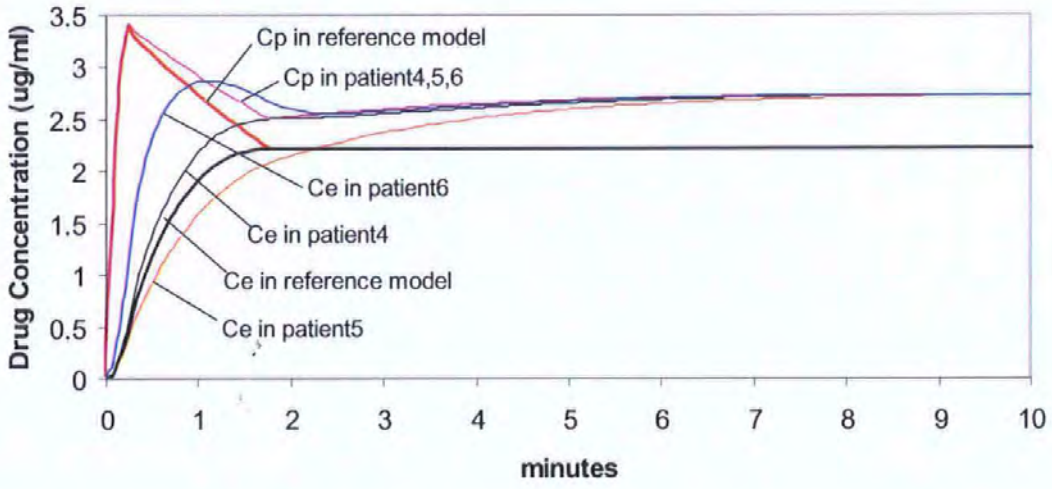


Figure 5-6 Drug concentrations of patient4, 5, and 6 in comparison with those predicted

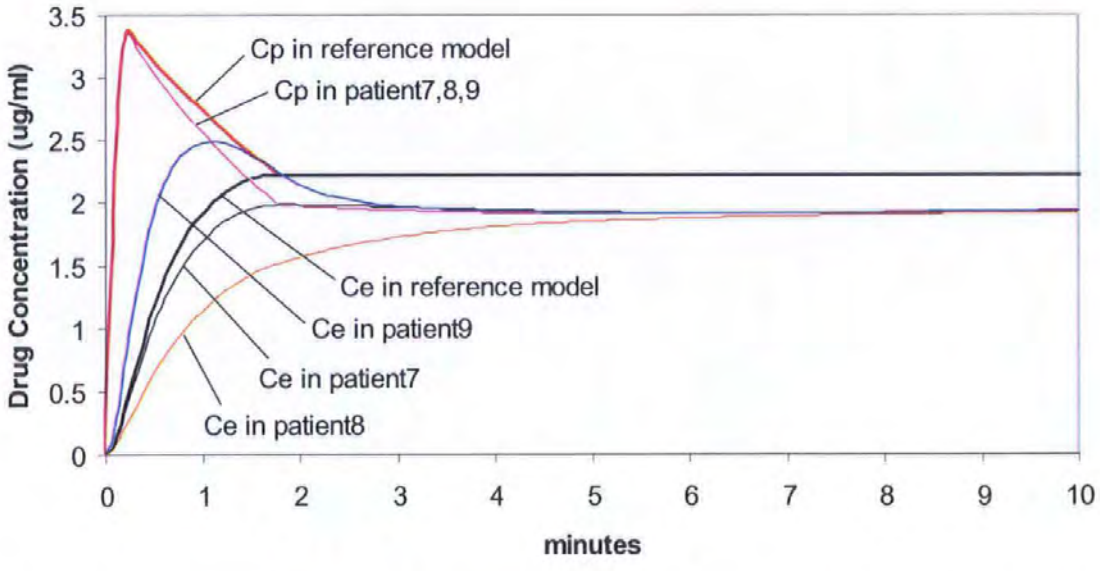


Figure 5-7 Drug concentrations of patient7, 8, and 9 in comparison with those predicted

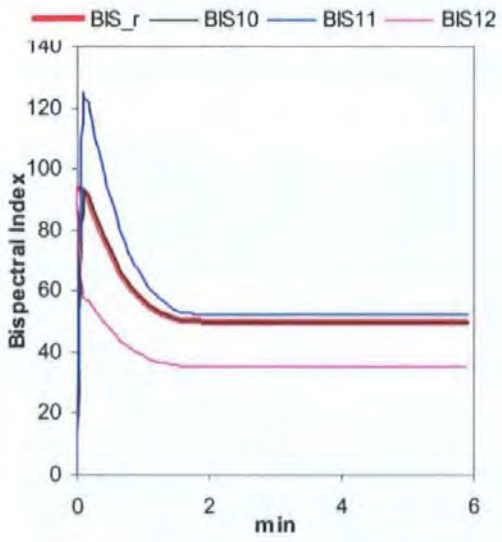
It can be seen from Figure 5-6 that the drug concentration profile of Patient1 is exactly the same as predicted by the reference model because the patient pharmacokinetic model is the same as the reference model. However, comparing to the reference model, Patient2 has a longer time for the infused drug to be transferred from plasma to effect site (2.4 minutes for drug effect peak time). At 1.7 minute, the effect site drug concentration in Patient2 is lower than predicted, and the low maintenance infusion rate from then slowly brings the effect site drug concentration up to the target at about 6.5 minute since then the drug concentrations in plasma and effect site equilibrate. For Patient3, the effect site drug concentration is higher than predicted at 1.7 minute due to the shorter peak time (1.0 minute) and the additional drug in the initial bolus for look-ahead compensation. It takes 1.3 minutes for the effect site drug concentration in Patient3 to fall to the equilibration concentration that is also the target concentration. Figure 5-5 also confirms the fact that the plasma drug concentration in the three virtual patients is identical as they have the same drug transfer rate constants.

Nevertheless, the actual responses from the rest of the patients are quite different from Patient1, 2, and 3 because they have pharmacokinetic characteristics other than those described by the reference model. Figure 5-6 shows the responses of Patient4, 5, and 6. Implied by the values of the rate constants in a pharmacokinetic model, the dominant rate constants are elimination rate constant (k_{10}) and the one describing drug transfer from the central compartment to the rapid compartment (k_{12}). Due to the smaller values of k_{10} and k_{12} in the pharmacokinetic models of Patient4, 5, and 6, the distribution loss of drug over time is over estimated by the reference model, and therefore the loss of drug in those patients gets over compensated and the equilibration drug concentration is then higher than the predicted (see Figure 5-6). Again, because of the difference in drug transfer delay (peak time) or hysteresis, the plasma and effect site drug concentration equilibrate at 1.7 minutes, 6.5 minutes, and 2.5 minutes for Patient4, 5, and 6, respectively. For Patient7, 8, and 9, on the contrary, the distribution loss of drug over time is under estimated by the reference model due to the larger values in k_{10} and k_{12}, and hence the loss of drug is under compensated for these patients that causes the equilibration drug concentration to be lower than the predicted (see Figure 5-7). The time for the plasma and the effect site drug concentration to equilibrate is 1.7 minutes, 6.5 minutes, and 3 minutes for Patient7, 8, and 9, respectively.

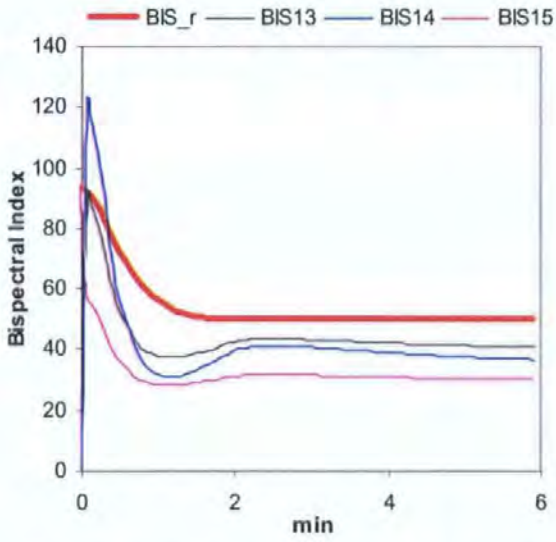
What about the patients whose drug distribution loss within a unit time (determined by the values of k_{10} and k_{12}) is within the range of that of Patient4, 5, 6, and Patient 7, 8, 9, or outside this range? Based upon the linear assumption of the pharmacokinetic model, we know that the equilibration drug concentration of these patients must be some values that are lower

than that of Patient4, 5, and 6, and higher than that of Patient7, 8, and 9, or outside this range. Under this TCI control scheme, any different values in peak time would only either slow down or speed up the equilibration of plasma and effect site drug concentration, and have no influence on the steady state effect site drug concentration maintained by the TCI system. Although most of the patients will be over or under compensated by the TCI system, the compensation infusion rate is too low or the amount of drug distribution loss is too small and it is in an exponential decay as time goes on. This guarantees that a stable equilibration drug concentration would eventually be maintained in any patient.

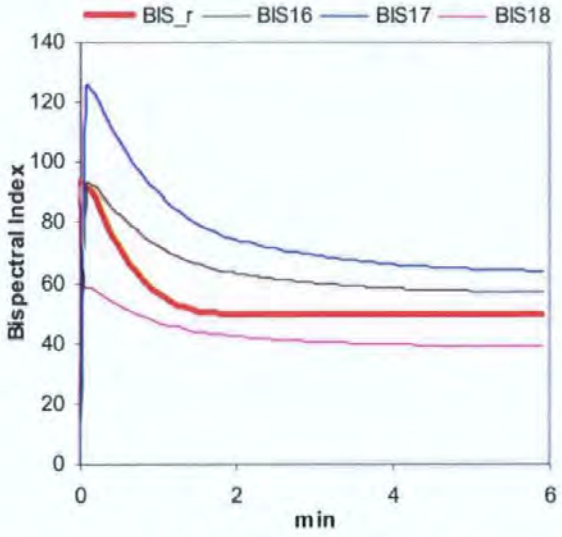
The results shown in Figure 5-5, Figure 5-6 and Figure 5-7 present the drug concentration response of intravenous drug delivery with presence of pharmacokinetic variability. For the investigation of pharmacodynamic variability, the pharmacodynamic model is used to obtain the Bispectral Index or the drug effect from propofol drug concentration. This investigation is carried out on the hypothetical patients Patient10~Patient18, and the results are presented in Figure 5-8 (a), (b), and (c).



(a) Drug effect in Patient10~Patient12



(b) Drug effect in Patient13~Patient15



(c) Drug effect in Patient16~Patient18

Figure 5-8 Drug effect in Bispectral Index in Patient10~Patient18 against the predicted effect (BIS_r is the BIS calculated by pharmacodynamic model from propofol drug concentration predicted by the TCI reference model, BIS*i* is the BIS calculated by pharmacodynamic model from propofol drug concentration predicted by the model of the i^{th} patient

Figure 5-8 shows the pharmacodynamic variability in patients (Patient10~Patient18) who have the largest pharmacokinetic variability within Patient1~Patient9. Figure 5-8 (a) presents the results from virtual patients with population average drug clearance rates and peak time, while Figure 5-8 (b) shows the results from patients with slower drug clearance rates and peak time, and the results from patients with faster drug clearance rates and peak time are demonstrated in Figure 5-8 (c). BIS_r is predicted by the built in population average PK/PD models. The steady state values of BIS_r are the desired BIS values, and various deviations from BIS_r can be seen from the BIS responses of Patient11~Patient18. However, these deviations can be minimised with the use of closed-loop control technique as will be seen in the following investigations.

5.5. Investigation of the CLAN System Model on Patient Variability

5.5.1. Methods

As discussed earlier, the built-in PK/PD models describe the drug distribution/effect of an average population and not for a specific individual patient. A real patient may therefore

respond to an anaesthetic drug in a different way from that described by the reference model (see Figure 5-5, Figure 5-6, Figure 5-7, and Figure 5-8) and a different stable level of anaesthesia other than that predicted by the reference model may be maintained in a patient. In this section, we will show how the proposed closed-loop anaesthesia or CLAN system will theoretically bring all the virtual patients to the desired level of anaesthesia without knowing the 'true' PK/PD characteristics of the patients, and the degree of variability of an individual patient's PK/PD against the population average.

Two investigations on the mathematical CLAN model have been carried out. One explores the behaviour of the CLAN model with existence of pharmacokinetic variability in hypothetical patients Patient1~Patient9, while the other looks at how the CLAN model handles the pharmacodynamic variability in virtual patients Patient10~Patient18.

The basic idea lying in the CLAN system is to minimise the difference between the actual stable equilibration drug concentration/effect and the predicted one seen in Figure 5-6, Figure 5-7, and Figure 5-8, and to speed up the equilibration for patients with large values in drug effect peak time (e.g., Patient2, 5, and 8). To achieve these goals, the PID controller modifies, in real time, the target drug concentration of a built-in TCI system that targets on mixed sites.

5.5.2. Investigation on Pharmacokinetic Variability

In clinical practice, the drug effect target would be changed up or down intra-operatively by the anaesthetist to meet the need of appropriate depth of anaesthesia in different stages of surgery. To simulate this dynamic requirement, BIS target in this investigation is changed down to an arbitrary value of 50 to achieve a deeper anaesthesia and is thereafter changed back to another arbitrary value of 65 before the infusion stops.

To achieve the best control performance, the PID controller gains designed in Section 6.5 were manually fine-tuned to individual patients, and the results are listed in Table 5-1. PID controller gains have significant influence on the performance of the CLAN system, and there are sets of gains for each patient from which the best control performance would be achieved. Table 5-1 lists one of them for each patient.

Table 5-1 Optimal PID controller gains for hypothetical patients of Patient1~Patient9

Patient	k_p	k_i	k_d
1	0.0024	0.000022	0.34
2	0.0015	0.000008	0.1
3	0.0012	0.00009	0.1
4	0.0012	0.00001	0.125
5	0.0024	0.00005	0.18
6	0.0024	0.00001	0.18
7	0.0019	0.00001	0.1
8	0.0024	0.00002	0.29
9	0.0008	0.00009	0.11

The effect site propofol drug concentration (Ce) and Bispectral Index (BIS) in the 9 hypothetical patients Patient1~Patient9 from this investigation are presented in Figure 5-9 and Figure 5-10.

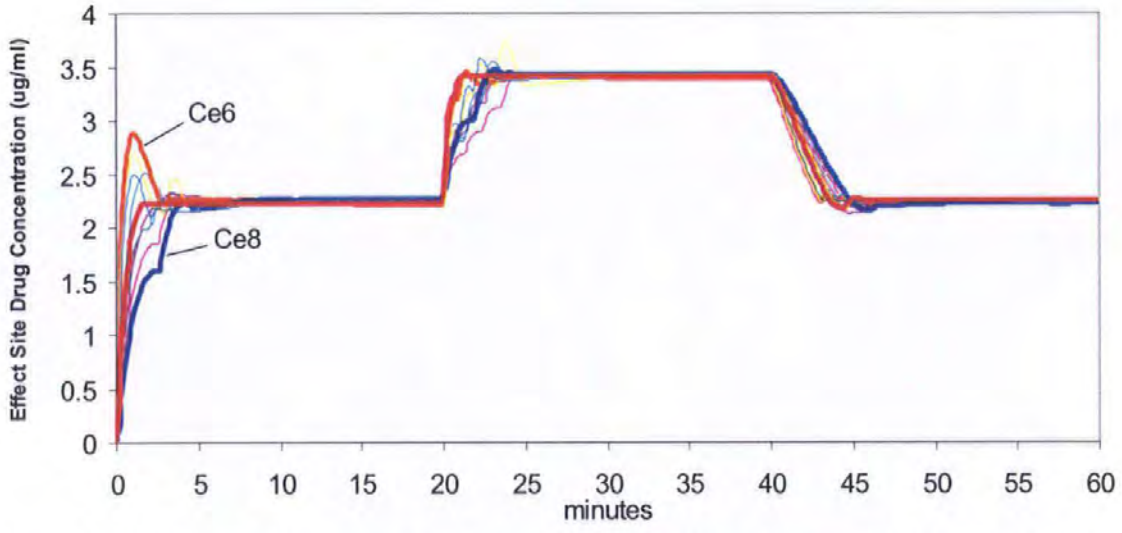


Figure 5-9 Effect site drug concentrations in Patient1~Patient9 controlled by the CLAN system using individual *optimal gains* (Ce6, Ce8: effect site drug concentration in Patient6 and Patient8, respectively)

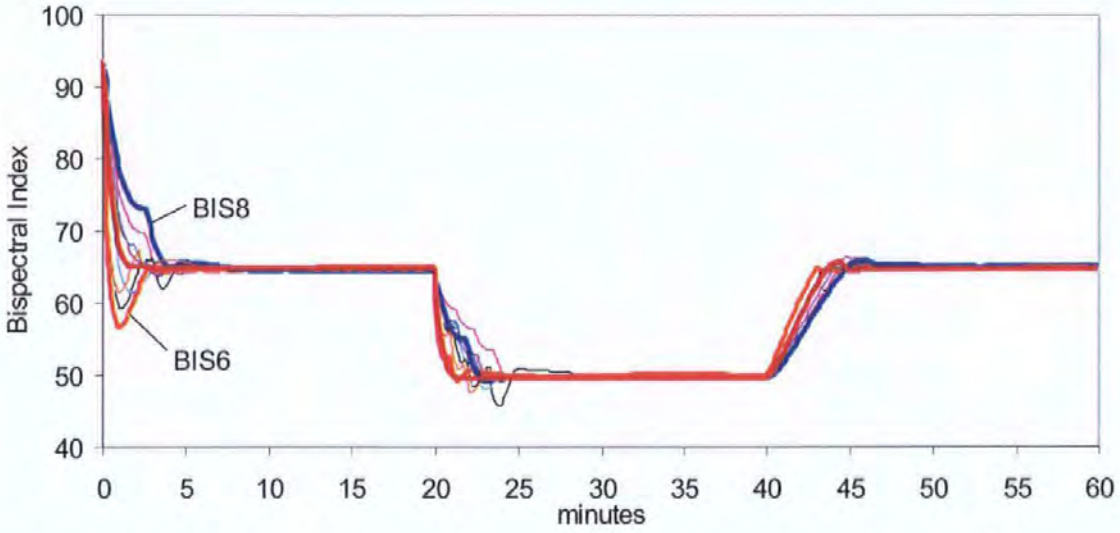


Figure 5-10 Bispectral Indexes in Patient1~Patient9 controlled by the CLAN system using individual *optimal gains* (BIS6, BIS8: Bispectral Index in Patient6 and Patient8)

All computer simulations start with the same initial bolus (ml/kg) infusion to all patients expecting to achieve the desired target in BIS, and then the infusion stops temporarily with active system monitoring on Bispectral Index that is calculated from the effect site drug concentration in the patient involved using population average pharmacodynamic model as shown in Table 4-5. Once the drug effect of the initial bolus reaches its maximum indicated by a peak value in BIS, the PID controller takes over the control and resumes drug infusion. If the value of BIS feedback indicates a lighter anaesthesia than the target, then the PID controller will decrease the target concentration of the built-in TCI system, otherwise the target concentration will be increased. Whenever the value of BIS feedback is close to the BIS target, the TCI system will target on effect site, and otherwise on plasma. Because the shortest cycle available from the anaesthesia monitor Aspect A-1000 is 5 seconds on which the Bispectral Index is updated, a new target concentration to the TCI system is generated from the PID controller in every 5 seconds.

After the bolus infusion and the change down in Bispectral Index target, the BIS falls quickly in some patients (e.g., Patient6) but slowly in others (e.g., Patient8), and there are Bispectral Index overshoots in some patients (e.g., Patient6) and undershoots in others (e.g., Patient8). However, the Bispectral Index target is quickly achieved and maintained in all hypothetical patients. It also shows that a period of time is needed for the CLAN system to re-achieve the target when it is changed.

5.5.3. Investigation on Pharmacodynamic Variability

This investigation is based upon the virtual patients Patient10~Patient18 in whom pharmacodynamic characteristics vary. However, the pharmacokinetic characteristics of Patient10~Patient12 inherit from Patient1 with population average parameter values, and those of Patient13~Patient15 are the same as that in Patient6 with least drug distribution loss (smallest drug clearance rates and shortest drug effect peak time) in Patient1~Patient9, while those of Patient16~Patient18 are identical to that in Patient8 with most drug distribution loss (largest drug clearance rates and longest drug effect peak time) in Patient1~Patient9. The PID controller gains for Patient1, 6, and 8 are also applied on Patient10~Patient18 as shown in Table 5-2. Apart from Patient10, the controller gains used might not be the optimal gains for all other patients due to the additional pharmacodynamic variability.

Table 5-2 PID controller gains for hypothetical patients of Patient10~Patient18

	k_p	k_i	k_d
Patient 10	0.0024	0.000022	0.34
Patient 11	0.0024	0.000022	0.34
Patient 12	0.0024	0.000022	0.34
Patient 13	0.0024	0.00001	0.18
Patient 14	0.0024	0.00001	0.18
Patient 15	0.0024	0.00001	0.18
Patient 16	0.0024	0.00002	0.29
Patient 17	0.0024	0.00002	0.29
Patient 18	0. 0024	0.00002	0.29

Because the BIS can never reach 65 from the pharmacodynamic model of Patient12, 15, and 18 listed in Table 4-6, the BIS target is therefore set to 50 in this investigation.

The results of this investigation are presented in Figure 5-11, and Figure 5-12. Figure 5-11 shows the effect site propofol drug concentrations in Patient10~Patient18, while Figure 5-12 presents the BIS responses from these patients.

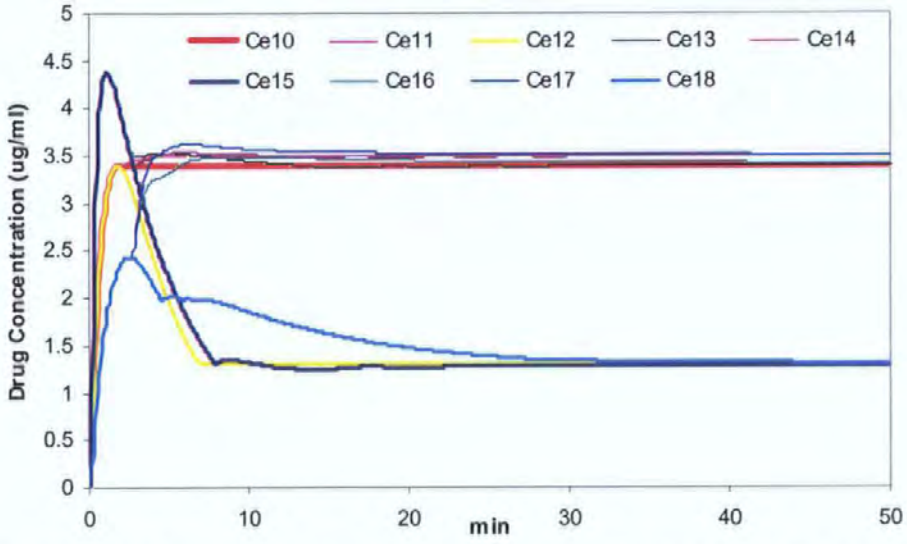


Figure 5-11 Propofol drug concentration in Patient10~Patient18 with PK/PD variability

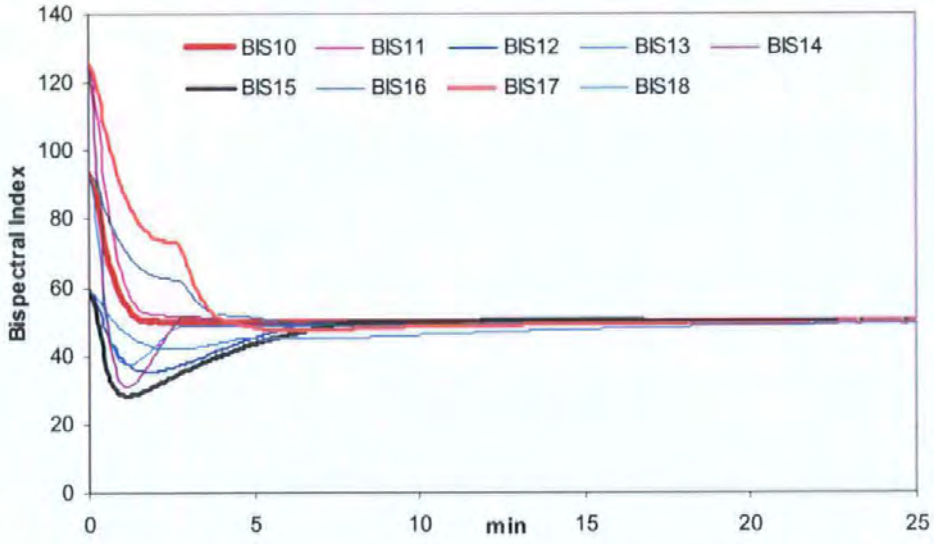


Figure 5-12 Bispectral Index responses in Patient10~Patient18 with PK/PD variability

As in the previous investigation, the simulations begin with the same initial bolus (ml/kg) infusion to all patients to achieve the BIS target, and the PID controller takes over the control when the drug effect peaks. Bispectral Index is calculated from the effect site drug concentration in patients using the pharmacodynamic models listed in Table 4-6. The same control scheme as used in the previous investigation is used here.

With pharmacodynamic varibility in Patient10~Patient18, although the BIS target is successfully achieved and maintained in all patients, the predicted effect site propofol concentrations in these patients are stabilised at different levels.

5.6. Discussion and Conclusion

By using optimal gains, the target Bispectral Index is achieved within 5 minutes either after the induction bolus infusion or after the change up/down of the target Bispectral Index.

In this chapter, the problems with regard to using a TCI system for drug infusion control have been investigated; it has also been investigated why there is patient variability, how this variability affects the drug administration, and finally how the developed CLAN system model solves these problems.

The investigation on TCI infusion control scheme in intravenous drug delivery identifies that targeting on mixed sites would achieve the best control performance. Targeting on plasma solely results in a stable drug concentration response at effect site with a long set-up time. However effect site targeting scheme achieves a quick but oscillatory response in effect site drug concentration (see Figure 5-1). The level of oscillation depends upon the drug effect peak time in the patient in question. The reason why the two targeting schemes result in different behaviours is that the drug infusion is continuous when targeting on plasma, whereas when targeting on effect site the drug infusion is intermittent as shown in Figure 5-2. Due to the instant peak of plasma drug concentration, drug is infused during every update cycle to compensate the drug distribution loss for the next cycle when targeting on plasma. However, when targeting on effect site, the effect site drug concentration reaches its peak 1.7 minutes after the drug is infused. To achieve the target drug concentration at effect site, extra drug must be infused to compensate the drug distribution loss over the 1.7 minutes. All drug infused to achieve the target is given in a bolus, and there is no drug infusion during majority period of time (see Figure 5-2).

The result from this investigation suggests that plasma could be targeted for the maintenance

of anaesthesia, while effect site could be used as the target site in induction of anaesthesia and whenever insufficient anaesthesia is indicated. Figure 5-3 shows the optimal open-loop drug infusion control performance when targeting on the mixed sites, and Figure 5-4 shows the history of infusion rates generated by this control scheme.

The patient variability has been thoroughly investigated using 18 hypothetical patients constructed from a published pharmacokinetic and pharmacodynamic parameter set. The investigation shows that the pharmacokinetic variability results in approximately a constant difference between the predicted effect site drug concentration by reference model and the actual drug concentration in a specific patient (see Figure 5-6 and Figure 5-7). When targeting on mixed sites, if the drug effect peak time is different from the population average value, this difference affects only the transient drug concentration response. The result of simulation on Patient1~3 (see Figure 5-5) shows the effect from drug effect peak time that is the only difference between the patients and the built-in reference PK/PD models.

In general, in comparison with the reference model, the shorter the peak time, or the smaller the drug elimination rate (k_{10}) and distribution rates (k_{12}, k_{13}), or the larger the redistribution rates (k_{21}, k_{31}), the more the system is susceptible to overshoot. The opposite is also true for undershoot.

While pharmacokinetic variability causes steady state difference between drug concentration predicted by the population average pharmacokinetic model and that in a specific patient, pharmacodynamic variability results in steady state difference between drug effect or Bispectral Index predicted by the population average pharmacodynamic model and that in a specific patient even if the effect site drug concentrations are the same. This is demonstrated in Figure 5-8(a) in which the results of investigation on Patient1~3 are presented. Because the pharmacokinetic parameters in Patient1~3 are identical to the population average values, only pharmacodynamic variability exists in Patient1~3 against the reference model.

When pharmacokinetic variability and pharmacodynamic variability co-exist in patients, the effect site drug concentrations and the drug effects in these patients should vary unless in rare cases the two types of patient variability interact so that the drug effects happen to be the same. The co-existence of pharmacokinetic and pharmacodynamic variability makes the drug effect more unpredictable as shown in Figure 5-8 (b) and (c).

Due to the introduction of closed-loop control technology, the CLAN system successfully achieves and maintains the target level of anaesthesia with either pharmacokinetic or

pharmacodynamic variability or the both. The steady state differences between the effect site drug concentrations in patients and those predicted by the reference model (see Figure 5-6 and Figure 5-7) disappear (see Figure 5-9), while the steady state differences between the drug effects in patients and those calculated by the reference models is no more existent (see Figure 5-12). In the CLAN system, the role of the PID controller is to minimize these differences as quickly as possible. After the PID controller takes over the infusion control, it examines the Bispectral Index of the patient against the target every 5 seconds. If the BIS value is less than the target (i.e., overshoot), it will stop (or not resume) the infusion until the BIS rises to the target. However, if the BIS value is larger than the target, the PID controller will generate a new target concentration that is higher than the previous one for the built-in TCI system, and the TCI system then decides which site should be targeted on and generates a new infusion rate for the next cycle. This process is clearly seen in the responses of Patient6 and Patient8 shown in Figure 5-10, and Patient15 and Patient17 shown in Figure 5-12.

In conclusion, the infusion control scheme of using mixed target sites shows great advantage in drug infusion control over that using a single target site. The patient variability causes problem for drug infusion controlled by TCI and needs human intervention to adjust the target concentration, while a closed-loop anaesthesia system has the ability to achieve any drug effect target with the presence of patient variability.

6. Design of Closed-loop Anaesthesia System

6.1. Introduction

Previously, a mathematical model based upon the system defined in Figure 4-1 has been developed, and the major potential problems associated with closed-loop anaesthesia control have been investigated using the model. To verify the developed mathematical model of closed-loop anaesthesia on real patients in typical clinical environment, a prototype of closed-loop anaesthesia control system was designed in the following sections and implemented. A real CLAN system is essential for further investigation of closed-loop anaesthesia because a number of assumptions are made in the mathematical model. In the design and implementation of the CLAN system, these assumptions were taken into consideration to cope with any possible non-linear behaviour of the system. The system to be designed includes both the open-loop path and the closed-loop path shown in Figure 4-1 for the infusion of alfentanil and propofol.

6.2. System Specifications

The specifications of the desired closed-loop control system consist of both hardware specifications and software specifications. The hardware specifications describe the physical components of the system available at the time the project started for this investigation, while the software specifications specifies the theoretical performance of the control system and are designed in the following sections.

6.2.1. Hardware Components and Interfaces

To carry out the CLAN investigation, a CLAN system consisting of the hardware components shown in Figure 6-1 was built. All necessary software device drivers were developed. The specifications of these available equipments are listed below:

Personal Computer:	120 MHz CPU
	4 RS-232 serial communication ports with an extra I/O card
	8 MB RAM
Anaesthesia Pump:	2 Graseby 3400 pumps with maximum infusion rate of 1200 ml/hour
EEG Monitor:	Aspect A-1000 EEG Monitor (with a digital signal converter)

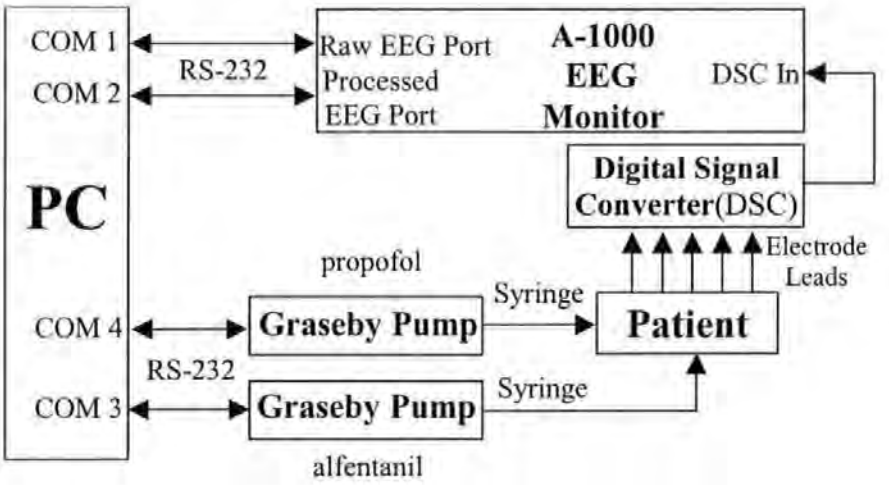


Figure 6-1 Physical components of the CLAN system

In this system, RS-232 RTS/CTS modem protocol is used for the host PC to control the pumps, while RS-232 null modem protocol is used to receive the data transmitted from the EEG monitor. The cables connecting the PC with the pumps and the monitor were made with the wiring described in Table 6-1, and the RS-232 serial communication protocols implemented in the CLAN system for the communications are shown in Table 6-2.

Table 6-1 RS232 Cable wiring between the PC, pumps, and EEG monitor

PC DB9(FEMALE) CONNECTOR	RAW EEG PORT DB9(FEMALE) CONNECTOR	PROCESSED EEG PORT DB9(FEMALE) CONNECTOR	GRASEBY 3400 PUMP DB9(FEMALE) CONNECTOR
2(RxD)	3(Data Out)	3(Data Out)	3(Data Out)
3(TxD)	2(Data In)	2(Data In)	2(Data In)
5(GND)	5(GND)	5(GND)	5(GND)
7(RTS)	No Connection	No Connection	8(Handshake In)
8(CTS)	No Connection	No Connection	6(Handshake Out)

Table 6-2 Serial communication protocols for the RS232 serial ports

PARAMETER	GRASEBY 3400 PUMP	A-1000 RAW EEG PORT	A-1000 PROCESSED EEG PORT
COM Port	COM4	COM1	COM2
Baud Rate	9600	19200	9600
Data Bits	8	8	8
Stop Bits	1	1	1
Parity	No Parity	No Parity	No Parity
Handshake	Hardware(CTS/RTS)	NO	NO

6.2.2. Sampling Period

Bispectral Index is calculated within the Aspect A-1000 EEG monitor based on the EEG waveform with a sampling frequency of 128Hz, however, the Bispectral Index is updated from the monitor at a selectable periods of 5, 10 or 15 seconds. To obtain the highest response speed from the CLAN system, 5 seconds update period was therefore used.

6.2.3. PID Controller

The specifications of the PID controller were given in time domain so that a search algorithm can be applied through computer simulation to find the desired controller gains. The specifications include rise time, maximum overshoot, settling time, and stead-state error as defined in Figure 3-5 in Section 3.2.2.

Because the CLAN system is safety critical, the fundamental requirement from a controller to be used in such a system is its response speed to any inadequate anaesthetic level. Based on this requirement, an aggressive rise-time of 50 seconds and a settling time of 75 seconds were chosen to obtain a reasonable fast response from the resulted PID controller since the drug effect peak time after a bolus infusion typically ranges from 1 to 2.4 minutes (Schnider et al., 1999).

Typical maximum overshoot for a PID controller is around 25%. In theory, a quicker response would be obtained from a larger maximum overshoot. However, this leads to a longer settling

time and results in more oscillation before the target has been achieved. This is not desired in a CLAN system using Bispectral Index which is not truly monotonic. Therefore a 10% maximum overshoot was set for the controller to compromise between the response speed and the smooth trend of Bispectral Index. As for steady state error, 10^{-3} is more than enough as Bispectral Index itself is oscillatory and the maximum measuring precision in Bispectral Index is 0.001.

6.2.4. Data Acquisition

Data acquisition is a software component in the CLAN system to collect and store the raw and processed EEG data sent from the from A-1000 EEG monitor, and to extract the Bispectral Index from the data stream. This involves with the implementation of the following functionality:

- RS-232 device driver for collecting data from raw/processed EEG ports
- One second period based raw EEG data packet real-time collection and storing
- Five seconds period based processed EEG data packet real-time collection and storing
- Synchronisation capture and reconstruction capability
- Bispectral Index (BIS) data extraction, processing, and storing

6.2.5. Anaesthesia Pump Control

To control the Graseby 3400 infusion pumps from the host PC, the following functionalities are required in the device driver:

- RS-232 communication driver
- Pump messages processing
- Regular infusion rate update

6.2.6. Patient Safety Control

As a safety critical medical control system, the CLAN system should be able to cope with any hazards they may happen. The following is a list of the functionalities the CLAN system should have:

- Switching between open-loop control and closed-loop control
- Emergency control
- Detect source of hardware failure and solve the problem if possible

- Capable of stopping, resuming and restarting infusion at any time
- Feedback signal quality control
- Warning messages
- Error Messages

6.2.7. User Interface

A user interface is required for the user to start/stop the drug infusion, and where necessarily to control the system externally. In case of the need to change syringe, pausing/resuming the drug infusion is required. When the quality of BIS data is bad or BIS is absent for a significant amount of time, the closed-loop control should be switched to open-loop control to protect the patient. Furthermore, the CLAN system should allow the user to change any patient specific parameters and the BIS target or target drug concentration.

A full list of the commands to be provided in the CLAN system is as follows:

- Starting, pausing, resuming and stopping infusion
- Syringe change
- Switching between open-loop control and closed-loop control
- Changing target site between plasma and effect site in open-loop control
- Changing some system parameters, such as controller gains, threshold values controlling stop and resuming infusion
- Changing closed-loop target
- Starting and stopping data storing
- Starting and stopping event logging
- Making or cancelling comment
- On-line searching logged event or comment
- Screen redrawing
- System exit

6.3. Data Acquisition

The Aspect A-1000 EEG monitor is used in the closed-loop control system to measure the drug effect or depth of anaesthesia from the EEG signal measured in patients. A number of EEG variables are calculated from the EEG signal within the monitor, which includes

Bispectral Index or BIS, spectral edge frequency, median frequency, and so on. A complete list of the variables calculated in the monitor is given in Table A-8-2. As discussed previously, BIS is fed back to the control system as the measure of the depth of anaesthesia. Every 5 seconds, the EEG monitor sends all the calculated EEG variables in a data packet to its Processed EEG Port in ASCII format. It transmits the digitised raw EEG binary data packet along with a copy of the processed EEG variables in another binary data packet to its RAW EEG Port every second. The sampling rate of the raw EEG signal is set to 128 samples per second on the monitor.

6.3.1. Packet Format from RAW EEG Port

Each packet from the raw EEG port starts with a header and ends with a checksum. Multi-byte numbers are transmitted least-significant byte or word first. The data packet shown in Table 6-3 contains the processed EEG variables for all the channels including the combined channels that are the average of either channel 1 and 2 or channel 3 and 4. The packet shown in Table 6-4 is the raw EEG data that consists of 4 channels of interleaved EEG data.

Table 6-3 Processed variables packet - 128 samples/second

Header (byte) = 0xab
Type (byte) = 5
Sequence Number (16 bits)
Host Revision Number (3 bytes)
DSC Revision Number (byte)
Artefact Flags for each of the 6 channels (4 bytes each); (4 measured channels + 2 combined channels)
Calculated Data for each of the 6 channels (25 variables (4 bytes each) per channel)
Checksum (16 bits)

Table 6-4 Raw EEG packet - 128 samples/second

Header (byte) = 0xab
Type (byte) = 2
Sequence Number (16 bits)
Raw EEG data, 4 channels interleaved
Checksum (16 bits)

Each raw EEG sample is a 16-bit 2's complement binary word with a range of +32767 to -32768 and a resolution of 0.050015 mV/unit. In the raw EEG packet, the raw EEG data from the four channels are interleaved, such that the first word is from channel 1, the second from channel 2, then channel 3, channel 4, and channel 1 again. The sampling rate of 128 samples per second makes the one-second-packet size of 1030 bytes in total. In the processed variable packet, after the transmission of the unique data pattern, the A-1000 sends the artefact flags indicating the types of artefacts (if any) detected within the previous cycle. The artefact flags are bit-mapped and listed in Table A-8-1. Each artefact flag word is a 32-bit unsigned integer. Following the artefact flags are all of the variables for channel 1, then all of the variables for channel 2, and so on. Each variable is a 4-byte IEEE single-precision floating-point value, and is listed in Table A-8-2. The appearance of the variables in the list shows the transmission order.

6.3.2. Data Format from Processed EEG Port

The processed EEG port transmits the processed data for 4 channels plus 2 channel pairs, along with impedance values, error codes, and a header record, in an ASCII format. This port can receive commands that alter the types of data to be transmitted.

There are four basic types of records transmitted by the processed EEG port:

- Header Record - describes each field of the Data Record
- Data Record - contains all processed EEG variables
- Impedance Record - contains impedance values from the impedance check
- Error Record - contains an error code

Each record starts with a unique string of characters, and ends with a Carriage Return (<CR>), followed by a Line Feed (<LF>) character. Fields within the records are delimited using the "pipe" character ("|", ASCII 7CH).

Impedance records are transmitted only when the impedance check is in progress and an error record is transmitted when an error is detected while header record is disabled. The examples of error record, impedance record and data record are shown in Appendix A.

The Data Record contains all of the processed EEG variables for the 4 channels plus 2 combined channels. The record starts with the current date and time (MM/DD/YYYY HH:MM:SS) and ends with a Carriage Return, followed by a Line Feed character. Following the information on system settings are the variables calculated from the channel 1 EEG signal and the artefact flags of the channel 1 during the last cycle, and then the variables and artefact flags for channel 2, 3, 4, 5, and 6. All variables except the artefact flags are right-justified decimal numbers. The 32-bit artefact flags and artefact detection enable words are represented as 8-digit hexadecimal numbers (see Appendix A for artefact flag definitions).

6.3.3. Implementation of Data Acquisition

In data communication between the PC and the RAW EEG port of the EEG monitor, the header, type, sequence number, host revision number and DSC revision number in the data packets form a unique data pattern and are therefore used for synchronisation. For processed EEG data communication, the current date is used as the synchronisation string. If synchronisation for any port is lost, then the contaminated binary data packet or ASCII data packet will be saved to an error file accordingly with time stamped (raweeg.err for raw EEG data packet containing errors and proeeg.err for processed EEG data with error). The reconstruction of synchronisation will take a minimum of one second for raw EEG port and five seconds for processed EEG port.

The data amount in binary data packets from raw EEG port is fixed (1030 bytes/second) while that in ASCII data packet from processed EEG port varies (maximum<2000 bytes) due to the possible error records and impedance records. Although the data transmission to the two ports is concurrent, the time needed to transmit the whole ASCII data packet is about 2.3 seconds. In implementation, therefore, we program the serial I/O ports of the PC to receive the incoming data continuously and to work in the background. The received data from both ports are stored in two large sizes of I/O port buffers that can hold at least five seconds data, and the buffered

data will be taken away for processing and archiving every five seconds. The size of the buffer holding binary data from raw EEG port is at least 1030.5=5150 bytes. However, the closed-loop system can not read the buffer on the basis of exact five-second period due to the busy work of the system. The maximum amount of buffered data is 8312 bytes, and the buffer size is set to 9300 bytes for this reason. For the data from processed EEG port, the closed-loop system reads the buffered data at the middle of the idle time of the port, that is 3.65 seconds from the beginning of a packet transmission, and the port buffer size is set to 2400 bytes. With 2.7 seconds idle time of the transmission port, this setting proves to be safe for the receiving of the processed EEG data.

Both the raw EEG data and processed EEG variables are stored in the PC for off-line analysis. Bispectral Index is extracted from the data stream to provide the feedback signal for the control system and is also stored under a dedicated directory. To avoid the large size of the data files, the incoming data are split into sections and stored in files under the dedicated directories according to the type of the data. For implementation of this strategy, each raw EEG data file contains only five minutes data, and each processed EEG data file contains the data of fifteen minutes while BIS file contains two hours data due to the low data rate. A data archive directory structure has been built for this purpose (Appendix B).

The real time data acquisition process is depicted in Figure 6-2.

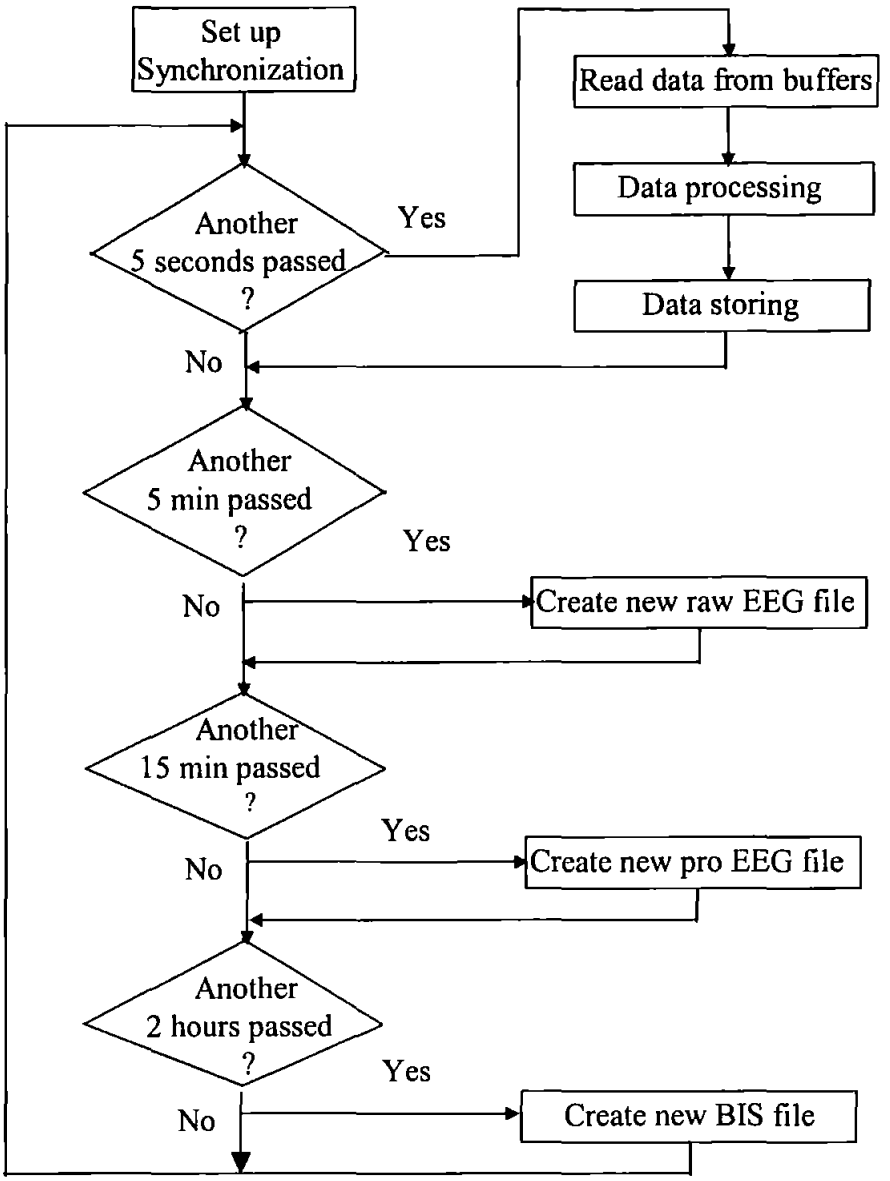


Figure 6-2 Flow diagram of data acquisition

6.4. *Target Controlled Infusion*

Target controlled infusion is used to control the two Graseby pumps and generate the infusion rates for hypnotic propofol and analgesic alfentanil. For each drug, a TCI with appropriate pharmacokinetic model is dedicated.

A TCI consists of a pharmacokinetic model, a drug infusion rate generator, and a pump driver. The block diagram of such a TCI is shown in Figure 6-3, where Cp (Ce) is the drug concentration in plasma (at effect site) predicted by the PK model, C_T is the target drug concentration, C is either Cp or Ce depending on the Target Site Control, ΔC is the difference between C and C_T, and I is the infusion rate to achieve the target concentration.

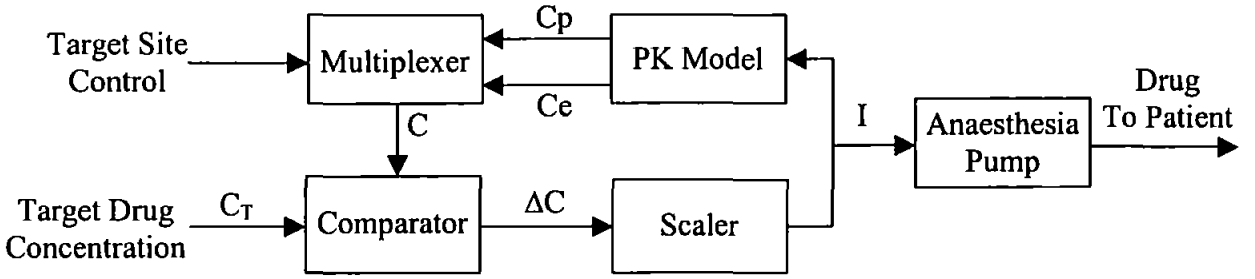


Figure 6-3 Block diagram of TCI open-loop system

In implementation of the above TCI system, part of the C code from freeware STANPUMP (Steven L. Shafer, Aneathesiology Service (112A), PAVAMC, 3801 Miranda Ave, Palo Alto, CA 94304, USA) is used with permission.

6.4.1. Implementation of Pharmacokinetic Model

The drug concentration estimation algorithm described in (Jacobs, 1990; Bailey and Shafer, 1991; Shafer and Gregg, 1992) is used for the implementation of the pharmacokinetic model.

Generally, for an *n*-compartment pharmacokinetic model where n is a positive integer, the theoretical calculation of plasma drug concentration defined in equation (2-2) could be rewritten in the following discrete form:

$$Cp_{CALC}(k) = T\sum_{m=0}^{k} I(m)D_p(k-m) \qquad (6\text{-}1)$$

If define a state variable $R_i(k)$ as follow

$$R_i(k) = \sum_{m=0}^{k} I(m)A_i e^{-\lambda i(k-m)T} \qquad (6\text{-}2)$$

then

$$Cp_{CALC}(k) = T\sum_{i=1}^{n} R_i(k) \qquad (6\text{-}3)$$

At time $(k+1)T$, the $R_i(k+1)$ can be calculated using (6-2)

$$R_i(k+1) = \sum_{m=0}^{k+1} I(m) A_i e^{-\lambda i(k+1-m)T} \tag{6-4}$$

Breaking the summation range, (6-4) can be expanded as

$$R_i(k+1) = \sum_{m=0}^{k} I(m) A_i e^{-\lambda i(k+1-m)T} + I(k+1) A_i \tag{6-5}$$

If the infusion rate over the period from t to t+Δt is a constant I, then

$$R_i(k+1) = e^{-\lambda i} \sum_{m=0}^{k} I(m) A_i e^{-\lambda i(k-m)T} + A_i I \tag{6-6}$$

This is equivalent to

$$R_i(k+1) = e^{-\lambda i T} R_i(k) + A_i I \tag{6-7}$$

Using equations (6-3) and (6-7), a recursive algorithm to calculate the plasma drug concentration can be derived as follows

$$Cp_{CALC}(k+1) = e^{-\lambda i T} Cp_{CALC}(k) + TA_i I \tag{6-8}$$

The first term in (6-8) represents the decay of the plasma drug concentration in the patient over the period from kT to $(k+1)T$ while the second term is the contribution from drug concentration by the drug infused at a constant infusion rate I over the same period. For three-compartment pharmacokinetic model (n=3), A_i can be obtained from equation (4-8) and (4-13), and λ_i are the roots of the characteristic equation (polynomial denominator) of $D_p(s)$ shown in equation (4-11), i.e., α, β, and γ, respectively.

Similarly, the algorithm to calculate the *effect site* drug concentration can be obtained

$$Ce_{CALC}(k+1) = e^{-\lambda i} Ce_{CALC}(k) + \sum_{i=1}^{n} B_i I \tag{6-9}$$

6.4.2. Infusion Rate Algorithm

As stated earlier, the drug infusion rate is generated from the target drug concentration and the drug concentration predicted by the population average pharmacokinetic model. Though the equations can be easily solved for infusion rate in the frequency domain, the implementation of these equations in the time domain are complicated, a modified Jacob algorithm (Jacobs, 1990) is therefore used in implementation.

If at time kT, the drug concentration is $Cp_{CALC}(kT)$ and a target concentration of C_T is given and required to be achieved at time $(k+1)T$. In original Jacob algorithm (Jacobs, 1990), as shown in Figure 6-4, two pharmacokinetic simulations are needed to work out the drug concentrations at $(k+1)T$ (i.e., $Cp_{CALC1}(kT)$ and $Cp_{CALC2}(kT)$) with two arbitrary infusion rates ($I_1(kT)$ and $I_2(kT)$) over the next period from kT to $(k+1)T$. Because of the linear relationship between the drug concentration gained and the amount of drug infused, the infusion rate to achieve the target concentration is easy to obtain from the line equation of the tilt line.

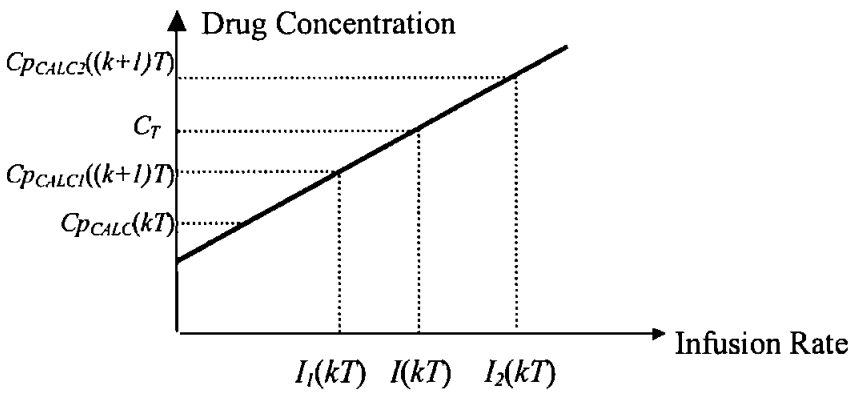


Figure 6-4 Original Jacob infusion algorithm ($I_1(kT)$, $I_2(kT)$: test infusion rates; $I(kT)$: infusion rate to achieve target concentration C_T)

The drawback of this algorithm is that the pharmacokinetic simulation has to be done twice at time kT and the slope of the line changes each time a new infusion rate is needed, therefore a modified infusion rate algorithm, which uses a fixed slope for all infusion rate updates and requires only one pharmacokinetic simulation at time kT, is used for instead. This algorithm is illustrated in Figure 6-5.

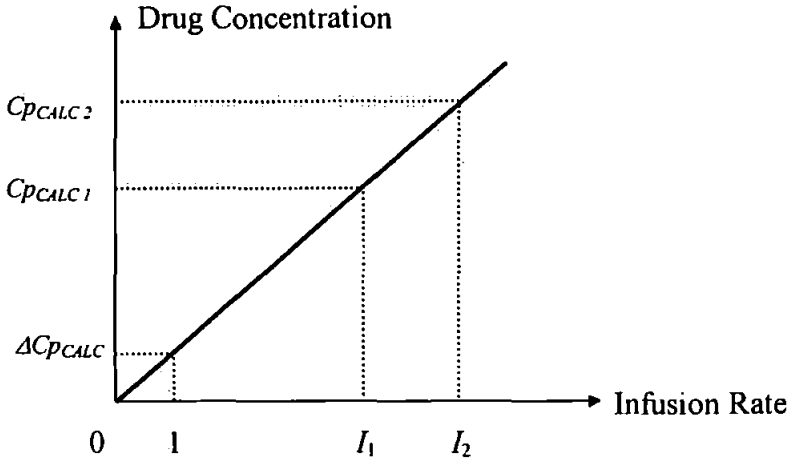


Figure 6-5 Modified Jacob infusion algorithm (I_1 and I_1: bolus infusion rates to achieve drug concentratioin Cp_{CALC1} and Cp_{CALC2} at time 0, respectively; ΔCp_{CALC} : unit drug concentration after the drug infusion with unit infusion rate of 1 ml/hour.kg at time 0 for T seconds)

This algorithm is based on the viewpoint at time 0 and before this time point zero drug concentration is assumed. At time 0, the drug concentration will be zero if there is no drug infusion, and if the infusion rate is 1 ml/hour.kg from time 0 to time T then the drug concentration will be ΔCp_{CALC}. Therefore a line (Figure 6-5) representing the relationship between an infusion rate and the resulted drug concentration can be drawn based on these facts. This relationship can be mathematically described by the line equation (6-10):

$$C_{pCALC} = \Delta C_{pCALC} \times I \tag{6-10}$$

where I is the infusion rate and Cp_{CALC} is the resulted drug concentration after T seconds.

Therefore, if the drug concentration needs to be increased from $Cp_{CALC}(kT)$ at time kT to $Cp_{CALC}((k+1)T)$ at time $(k+1)T$, the infusion rate can be calculated by (6-11) which is derived from (6-10):

$$I(kT) = \frac{C_{pCALC}((k+1)T) - C_{pCALC}(kT)}{\Delta C_{pCALC}} \tag{6-11}$$

6.4.2.1. Targeting on Plasma

Considering that the drug concentration at time kT will decline while drug is being infused during the next period, the compensation is therefore needed for this drug loss. Suppose the plasma drug concentration at time kT is estimated as $Cp_{CALC}(kT)$, and at time $(k+1)T$ the drug concentration will decline to $Cp_{CALC}((k+1)T)$ if no drug is infused over the period from kT to

$(k+1)T$. This can be obtained from pharmacokinetic simulation at time kT. Hence the infusion rate to achieve target plasma concentration $C_T(kT)$ at time kT can be calculated from (6-12):

$$I(kT) = \frac{C_T(kT) - C_{pCALC}((k+1)T)}{\Delta C_{pCALC}} \tag{6-12}$$

Theoretically, any plasma target concentration could be achieved and maintained using this infusion algorithm. To achieve the target concentration in anaesthesia induction, a single initial bolus is required and the bolus infusion rate $I(0)$ could be calculated with the zero initial condition $Cp_{CALC}(1)=0$.

As the unit plasma drug concentration or scale factor ΔCp_{CALC} is calculated on the basis of sampling period T, the infusion rate update period should also be set to the same constant T to avoid loss of accuracy.

6.4.2.2. Targeting on Effect Site

Although the infusion rate generation algorithm for targeting on plasma is simple, the one for targeting on effect site is more complicated because of the hysteresis of drug effect after drug infusion. When effect site becomes the site of target, the infusion rate given to the anaesthesia pump is supposed to result in a peak effect site concentration that is equal to the target drug concentration. This implies that iterations of calculating the effect site drug concentration with incremental infusion rates are required.

Suppose no previous drug infusion has been given. The unit effect site drug concentration (ΔCe_{CALC}) is similarly defined as the maximum effect site concentration at peak time ($t_p=NT$) after the infusion with a unit infusion rate of 1 ml/hour over a sampling period T. Here NT is the initial drug effect peak time that is equal to the population average peak time of 1.7 minutes. Using the same method as used for calculating the infusion rate when targeting on plasma, the infusion rate $I(k)$ over a sampling period T would be

$$I(kT) = \frac{C_T(kT) - Ce_{CALC}((k+n)T)}{\Delta Ce_{CALC}} \quad \text{and} \quad \Delta Ce_{CALC} = \frac{17.05}{w} \tag{6-13}$$

Where $C_T(k)$ is the target concentration at effect site at time kT, and $Ce_{CALC}(k+n)$ is the peak effect site drug concentration at time $(k+n)T$ where n varies and depends on the drug concentration at time kT and the infusion rate $I(k)$ to be given. ΔCe_{CALC} can be obtained from either simulation or mathematical integration, and w is the weight of the patient.

To solve the equation (6-13) for $I(k)$, a recursive search mechanism for the dynamic number n is used. It is worth noting that equation (6-12) is actually a special case of equation (6-13) with n=1, and that there will be no further infusion between $(k+1)T$ and $(k+n)T$ if the target concentration remains unchanged during this period.

The recursive search algorithm for infusion rate is shown in the following flow chart.

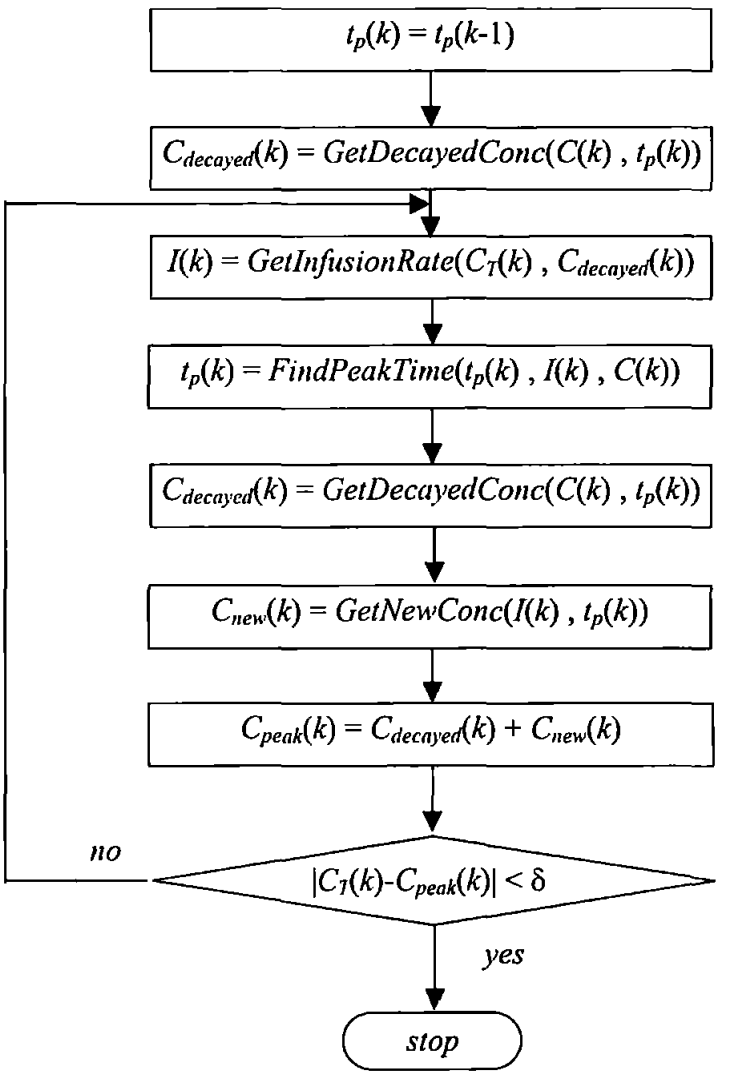


Figure 6-6 Flow chart of the infusion rate generation algorithm for targeting on effect site

In above flow chart, $t_p(k)$ is the drug effect peak time estimated at time kT, while $t_p(k\text{-}1)$ is previous peak time estimated at time $(k\text{-}1)T$. $I(k)$ is the infusion rate to be given at time kT, $C(k)$ is the effect site concentration at time kT, and $C_T(k)$ is the target effect site concentration

at time kT. $C_{decayed}(k)$ is the effect site drug concentration after decay over the period of time of $t_p(k)$ without infusion but estimated at time kT. $C_{new}(k)$ is the peak effect site drug concentration after T-second drug infusion if no drug has been infused before this. $C_{peak}(k)$ is the peak effect site drug concentration after $t_p(k)$ but estimated at time kT. Due to the linear assumption, $C_{peak}(k)$ is the sum of $C_{decayed}(k)$ and $C_{new}(k)$. δ is a small constant and used for controlling the precision of the infusion rate generation. Functions *GetDecayedConc( )* and *GetNewConc( )* are the implementation of the first and second term of the equation (6-9), respectively, while function *GetInfusionRate( )* is the implementation of equation (6-13). The function *FindPeakTime( )* implements a numeric search algorithm based on the estimated effect site drug concentration and infusion rate at time kT.

6.5. PID Controller

6.5.1. Design Method

The PID controller is used in the CLAN system for updating the target concentration of the TCI controlling infusion of hypnotic agent propofol. The closed-loop path of the CLAN system described by Figure 4-1 is redrawn in Figure 6-7 for the purpose of PID controller design.

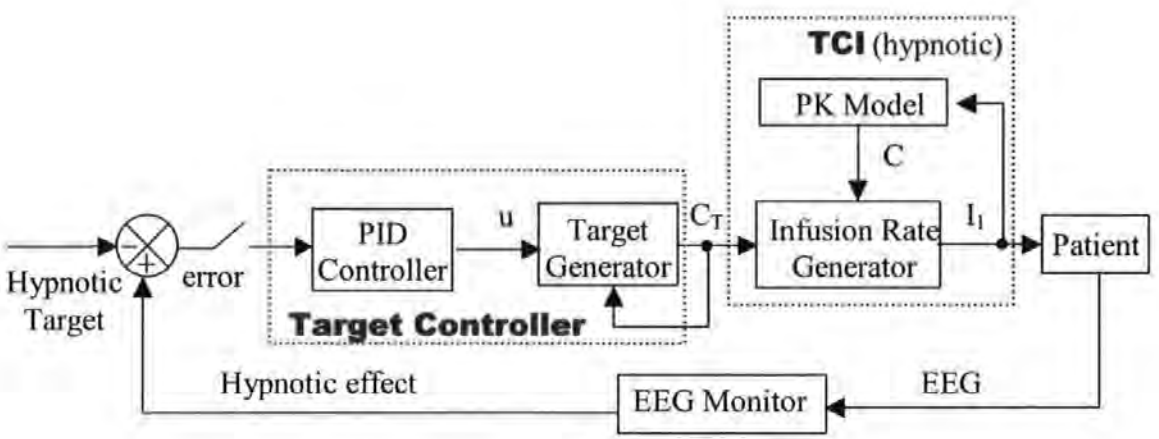


Figure 6-7 The closed-loop path of the CLAN system described by Figure 4-1

However, the order of this system is quite high due to the two pharmacokinetic models (reference model in the TCI and patient model). Instead of designing the PID controller in a high-order system, a simpler closed-loop system shown in Figure 6-8 is designed, and then the controller gains are converted into those that can be used in the system shown in Figure 6-7 or Figure 4-1 with the same control performance.

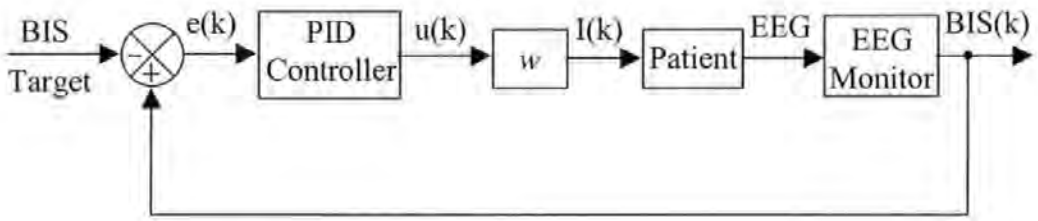


Figure 6-8 Direct PID controlled closed-loop anaesthesia system
(w is the weight of the patient)

In the closed-loop system shown in Figure 6-8, the PID controller directly gives the infusion rate, no pharmacokinetic model is used for the infusion control, hence no target drug concentration involves explicitly.

Suppose $u_1(k)$ is the output of the PID controller in Figure 6-7, and $u_2(k)$ is that in Figure 6-8, rewriting (6-13) to (6-15) gives

$$I(k) = 0.05865w(C_T(k) - Ce_{CALC}(k+n)) \qquad (6\text{-}15)$$

This implies that for any change of target drug concentration made by $u_1(k+n)$ in the target generator when $Ce_{CALC}(k+n) = C_T(k)$, the pump will infuse drug with infusion rate of $0.05865wu_1(k)$ during the next T seconds. For the desired closed-loop system (Figure 6-7) to have the same transient and steady state characteristics as the direct PID closed-loop control system (Figure 6-8), the infusion rates generated by the two systems from the identical error should be the same. This results in the following relationship between the two systems:

$$wu_2(k) = 0.05865wu_1(k) \quad \text{or} \quad u_1(k) = 17.05u_2(k) \qquad (6\text{-}16)$$

If k_{p1}, k_{i1} and k_{d1} are the PID controller gains in the system shown in Figure 6-7, and k_{p2}, k_{i2} and k_{d2} are those in the system shown in Figure 6-8, then (6-16) implies

$$k_{p1} = 17.05 k_{p2} \quad k_{i1} = 17.05 k_{i2} \quad k_{d1} = 17.05 k_{d2} \tag{6-17}$$

The PID controller gains were obtained using the following method:

1. Estimate initial gains (k_{p1}, k_{i1} and k_{d1}) for the system shown in Figure 6-7 from system response specifications defined Section 6.2.3

2. Convert these gains into the gains (k_{p2}, k_{i2} and k_{d2}) in the system shown in Figure 6-8 using (6-17)

3. Using repeatedly computer simulation, search for the best set of gains which meets the specifications of system response

4. Evaluate the searched controller gains using Bode diagram, root locus, and the unit step response

5. Convert the gains k_{p2}, k_{i2} and k_{d2} back into the gains k_{p1}, k_{i1} and k_{d1} using (6-17), and use manual adjustment to refine the gains

6.5.2. Estimation of Initial Gains

PID controller gains can be initially estimated from the system specifications, i.e. rise time, steady state error, and the relationship between the drug concentration and BIS effect. From (4-28), the following relationship exists between the change in drug concentration and the change in BIS.

$$\Delta C = -\Delta BIS / 12.837 \tag{6-18}$$

Suppose the system shown in Figure 6-7 has been at steady state before time kT without steady state error, if the Bispectral Index was increased by 1 (anaesthesia becomes lighter) at time kT, then this relationship suggests that the drug concentration must have been decreased by $-1/12.837$ μg/ml or -0.0779 μg/ml at the same time. Therefore, the PID controller is supposed to increase the target concentration for the pharmacokinetic model to compensate this loss in concentration, i.e. $u(k)$=0.0779 μg/ml, and consequently increase the BIS value by 1. However, this compensation should be spread over 50 seconds (rise time) or 10 sampling periods because of the hysteresis of drug effect with target concentration increased by 0.0779/10 or 0.00779 μg/ml at each cycle on average. Because the main contribution to the extra target concentration is from proportional term, therefore, $k_{p1} \times e(k) \approx 0.00779 \times e(k)$ or $k_{p1} \approx 0.00779$.

For estimation of the integration gain, the following assumption was made: the minimum contribution to the extra target concentration should be made when the steady state BIS error has been accumulated to 1. Because the BIS precision is 0.001, so $k_{i1} \times 1 \approx 0.001/12.837$ or $k_{i1} \approx 7.79 \times 10^{-5}$.

Derivative term in the PID controller made its contribution to the extra target concentration only when the rate of BIS error changes even if an outstanding BIS error is present. Once the rate of change and the error are both positive, it indicates that the anaesthesia starts to become inadequate at a significant speed. Because this is a one-off anticipated contribution, this contribution should be large enough to stop this trend as soon as possible.

Considering a BIS error of 5 occurs at steady state without steady state error, the proportional term will add $k_{p1} \times error = 0.00779 \times 5$ or 0.03895 μg/ml to the target concentration at current cycle, and will contribute at least 0.03895×10 μg/ml in total (as the BIS error will keep growing due to the hysteresis) within the next 50 seconds (rise time, 10 sampling periods) as aforementioned. Clearly, the contribution from the proportional term at this cycle is far less than enough to stop the rise of BIS. Therefore, a one-off contribution, as large as the minimum contribution from the proportional term (0.03895×10 μg/ml), from the derivative term seems to be a reasonable start for the estimation of the initial derivative gain. Because the system is assumed at steady state with zero error when the BIS rise happens, so the initial derivative gain can be estimated as follows based on (4-32).

$k_{d1} \times \frac{(5-0)-(0-0)}{T} \approx 0.03895 \times 10$ or $k_{d1} \approx 0.3895$, where T is the sampling period of 5 seconds.

In summary, the gains of the PID controller of the system shown in Figure 6-7 have initially been estimated from the specifications as the following values.

$$k_{p1} \approx 0.00779 \qquad k_{i1} \approx 7.79 \times 10^{-5} \qquad k_{d1} \approx 0.3895 \tag{6-19}$$

6.5.3. Search of Optimal Gains

Considering the infusion rate $I(k)$ is proportional and $H_p(s)$ is inversely proportional to the weight (w) of the patient involved, the mathematical model of the control system shown in Figure 6-8 is shown in Figure 6-9 with EEG Monitor replaced by the population average pharmacodynamic model.

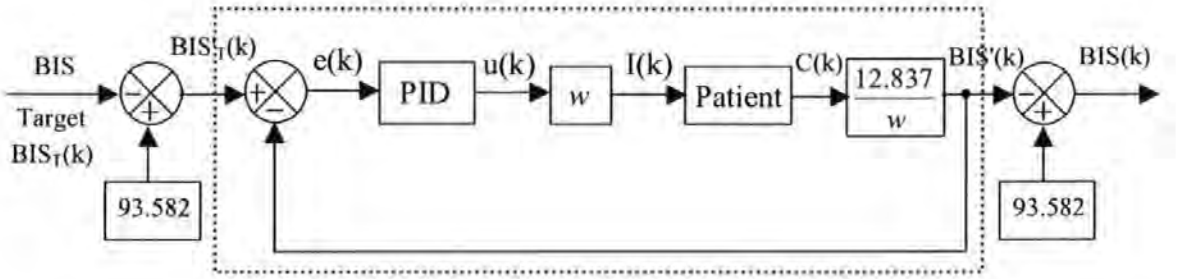


Figure 6-9 The mathematical model of the control system shown in Figure 6-8

The discrete transfer function representation of the closed-loop system within the dotted rectangle is shown in Figure 6-10.

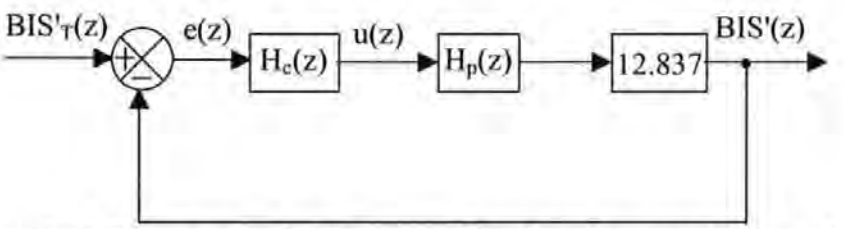


Figure 6-10 Discrete transfer function of the dotted system in Figure 6-9 (this closed-loop system is no longer associated with the patient weight)

By using (6-17), the initial PID controller gains in the system shown in Figure 6-10 are obtained as follows.

$$k_{p2} \approx 4.57 \times 10^{-4} \qquad k_{i2} \approx 4.57 \times 10^{-6} \qquad k_{d2} \approx 0.0228 \tag{6-20}$$

The simplified system shown in Figure 6-10 was implemented in MATLAB environment, and simulations were run repeatedly with specified PID controller gains to search all possible set of gains that meet the specifications specified in Section 6.2.3 (i.e. the maximum overshoot, rise time and steady state error).

In order not to miss any valid gains, a downward search was performed within the range specified in Table 6-5 with search steps shown in the same table. In each run of the simulation, only one of the three gains was changed.

The actual values of the parameters describing system performance, i.e. the maximum overshoot, rise time and steady state error, were stored together with the associated gains that

meet the specifications. When the search finished, all stored gains were examined again to search for the gains with the best performance.

Table 6-5 Parameters for PID controller gain search

	k_p	k_i	k_d
Start value	100×10^{-5}	100×10^{-7}	0.1
Search step	10^{-5}	10^{-7}	0.001
End value	0	0	0

After the simulation, following gains were found through the search algorithm:

$$k_{p2} = 3.9\times10^{-4} \qquad k_{i2} = 3.7\times10^{-6} \qquad k_{d2} = 0.028$$

With further tuning by hand, the following optimal gains were obtained for the system shown in Figure 6-8:

$$k_{p2} = 3.895\times10^{-4} \qquad k_{i2} = 3.7\times10^{-6} \qquad k_{d2} = 2.843\times10^{-2} \tag{6-21}$$

This results in the PID controller discrete transfer function represented in (6-22)

$$H_c(z) = \frac{0.006085z^2 - 0.011754z + 0.005687}{(z-1)z} \tag{6-22}$$

6.5.4. Gain Evaluation

The patient model in Figure 6-10 should be the model of a patient with unit weight (i.e., 1 *kg*). Since the PID controller was designed in z-domain, the conversion of patient model ($H_p(s)$ in equation (4-24)) in s-domain to z-domain ($H_p(z)$) is required. This can be done by inserting a zero-order hold (ZOH) before the continuous time controlled object. The transfer function of the ZOH is $\frac{(1-e^{-Ts})}{s}$, which should be absorbed by and discretised along with the patient model in the form of

$$H_p(z) = (1 - z^{-1}) \square \left(\frac{H_p(s)}{s} \right)$$

The conversion is done through bilinear transformation with the following population average pharmacokinetic parameters (time unit of second is used instead of minute):

$k_{10} = 0.002533$/sec,

$k_{12} = 0.00345$/sec,

$k_{13} = 0.00067$/sec,

$k_{21} = 0.00153$/sec,

$k_{31} = 0.00008$/sec,

k_{e0} = 0.00865/sec (calculated from the drug effect peak time of 1.7 minutes in pharmacokinetic simulation),

$V_1 = 0.159w$ ml, where w is the weight (kg) of the patient

$T = 5$ seconds (sampling period),

This bilinear transformation gives

$$H_p(z) = \frac{0.81813z^5 + 0.82471z^4 - 1.62311z^3 - 1.63626z^2 + 0.80499z + 0.81156}{z^5 - 3.91707z^4 + 5.75306z^3 - 3.75491z^2 + 0.91892z}$$

Hence the numerator vector and the denominator vector of the patient model are

numd = [0.81813 0.82471 –1.62311 –1.63626 0.80499 0.81156]

dend = [1 –3.91707 5.75306 –3.75491 0.91892 0]

The open-loop Bode diagram, root locus, and the closed-loop (no PID controller) unit step response can be obtained with the following MATLAB functions:

```
[mag, phase, w] = dbode(numd, dend, T);
margin(mag, phase, w);
figure; rlocus(numd, dend);
[numd, dend] = feedback(numd, dend, 1, 1);
figure; dstep(numd, dend, 40);
```

The Bode diagram (negative gain and phase margins), root locus, and the unit step response of the system excluding the PID controller all indicate an unstable closed-loop system if no compensation to the system is made.

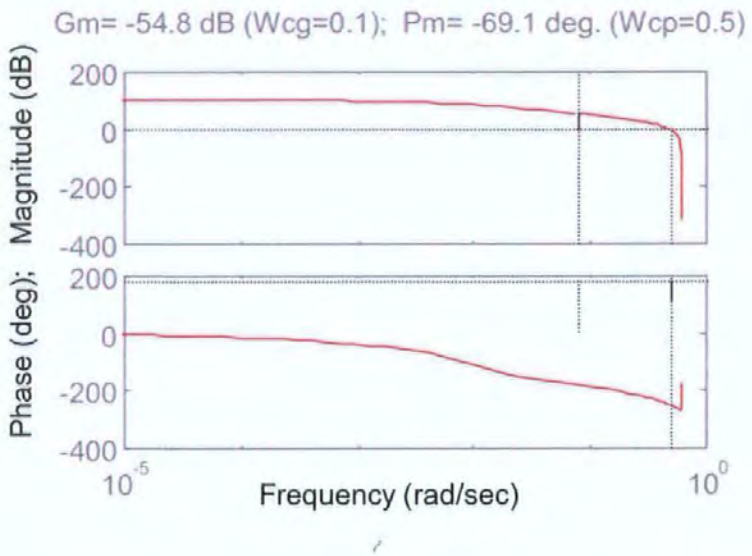


Figure 6-11 The Bode diagram of the system in Figure 6-10 without PID controller

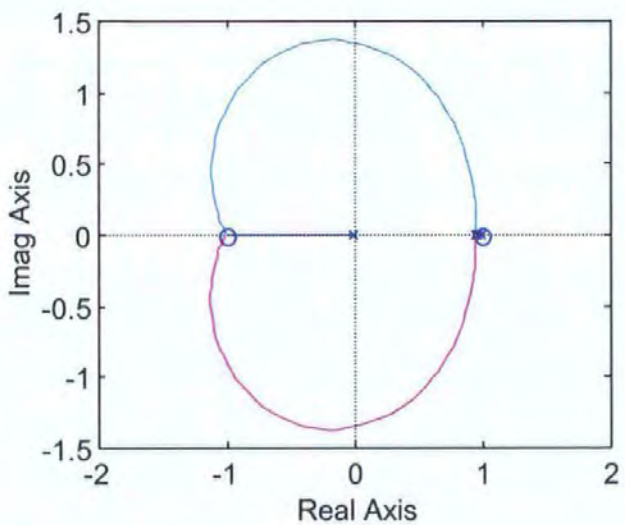


Figure 6-12 The root locus of the system in Figure 6-10 without PID controller

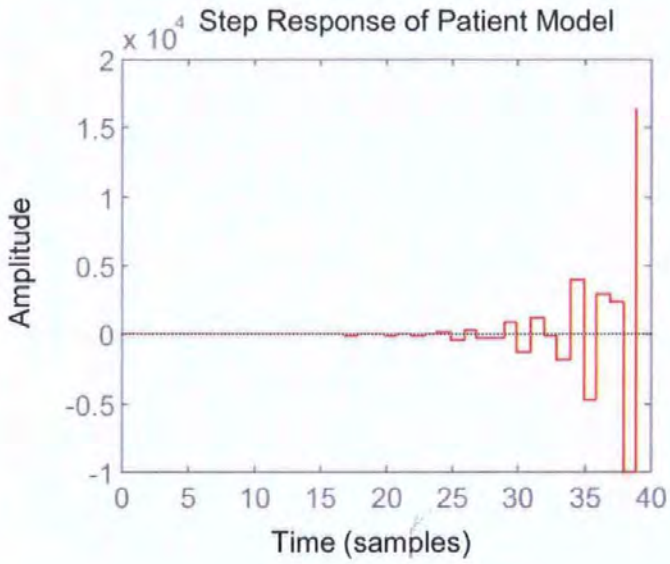


Figure 6-13 The unit step response of the system in Figure 6-10 without PID controller

By using the following vectors obtained from (6-22), the Bode diagrams and the root locus of this PID controller are drawn in Figure 6-14 and Figure 6-15, respectively.

numc = [0.006085 -0.011754 0.005687];

denc = [1 –1 0];

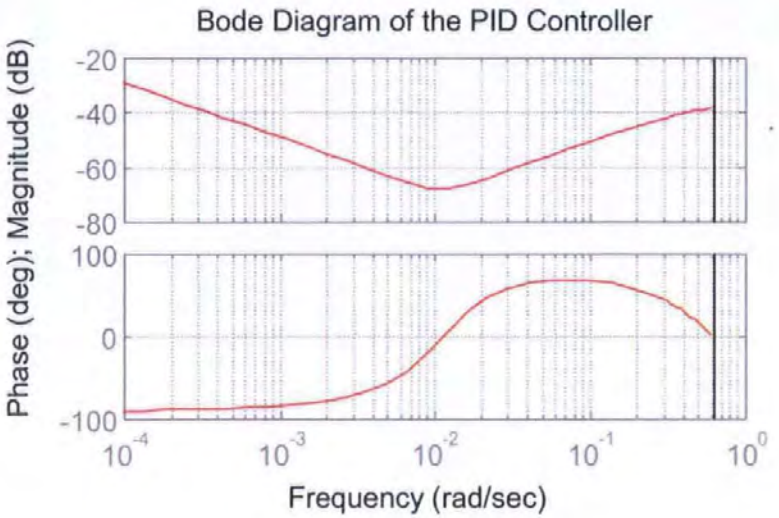


Figure 6-14 The Bode diagram of the designed PID controller

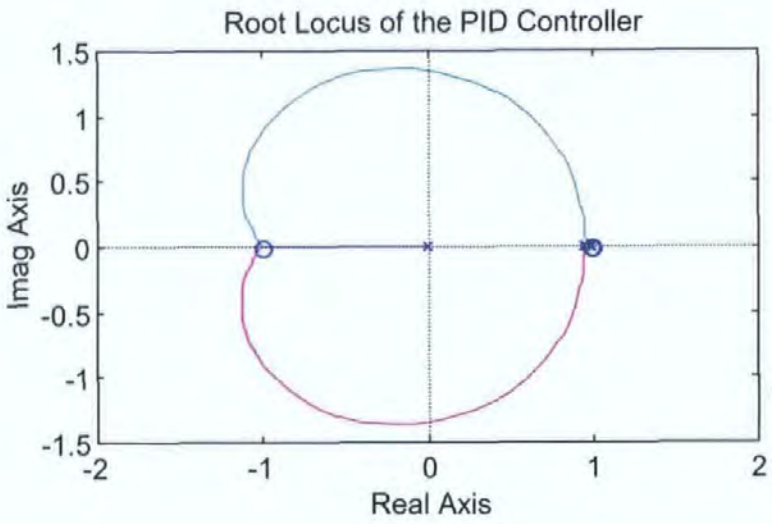


Figure 6-15 The root locus of the designed PID controller

Hence the new open-loop pulse transfer function can be formed by the following MATLAB function

[numd, dend] = series(numc, denc, numd, dend)

The Bode diagram, root locus, and unit step response of the compensated closed-loop control system can be obtained by the following MATLAB functions and are shown in Figure 6-16, Figure 6-17, and Figure 6-18:

```
[mag, phase, w] = dbode(numd, dend, T);
margin(mag, phase, w);
figure; rlocus(numd, dend);
[numd, dend] = feedback(numd, dend, 1, 1);
figure; dstep(numd, dend, 120);
```

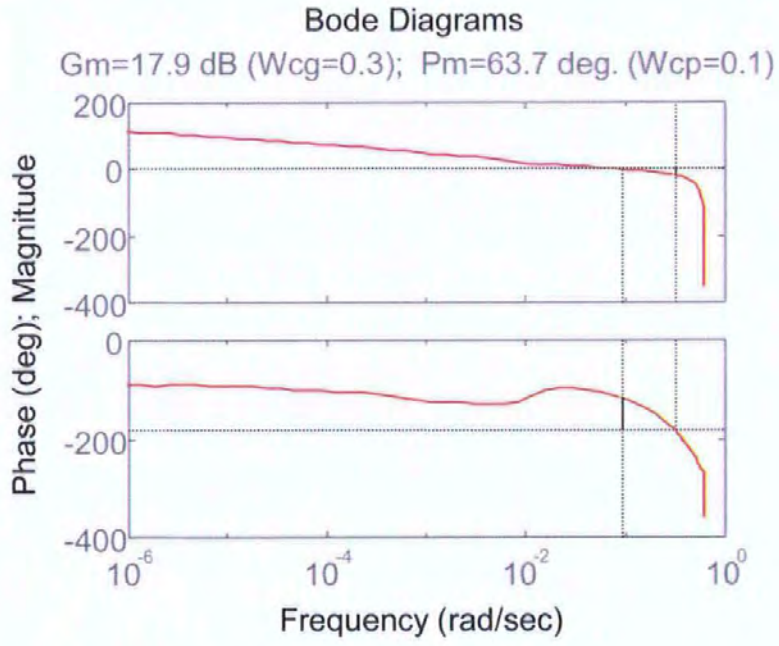


Figure 6-16 The Bode diagram of the compensated system

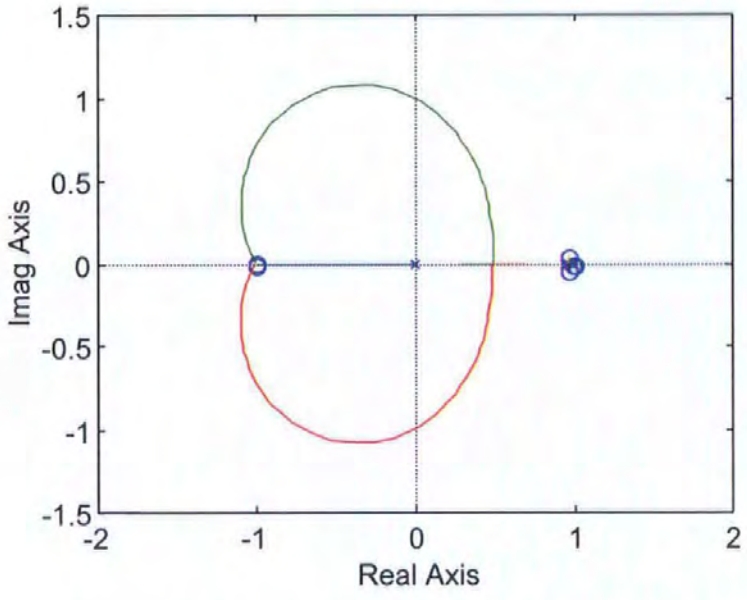


Figure 6-17 The root locus of the compensated system

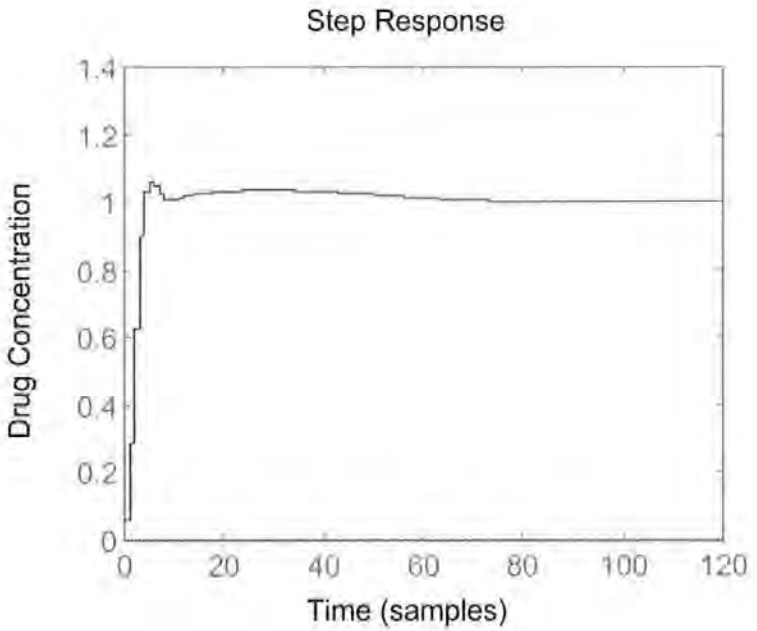


Figure 6-18 The unit step response of the closed-loop PID control system

From the results shown by Figure 6-16, Figure 6-17, and Figure 6-18, one could see the designed PID control system has a good performance with gain margin of 17.9dB and phase margin of 63.7deg. The system has a quick rise time (5 samples or 25 seconds) and settling time (8 samples or 40 seconds) with steady state error of 1.17e-007. The maximum overshoot of the system is 6%. They all meet the system specifications expected before the design.

One can easily simulate the designed system with any BIS target using the following MATLAB code. Figure 6-19 shows an example for the BIS target of 65.

```
BIS_Target = 65; N = 100; k = 0:N-1;
CT = (93.582 - BIS_Target)/12.837;
X = CT.ones(1,N);
Y = filter(numd,dend,X);
BIS = -12.837.Y + 93.582;
plot(k,BIS);
```

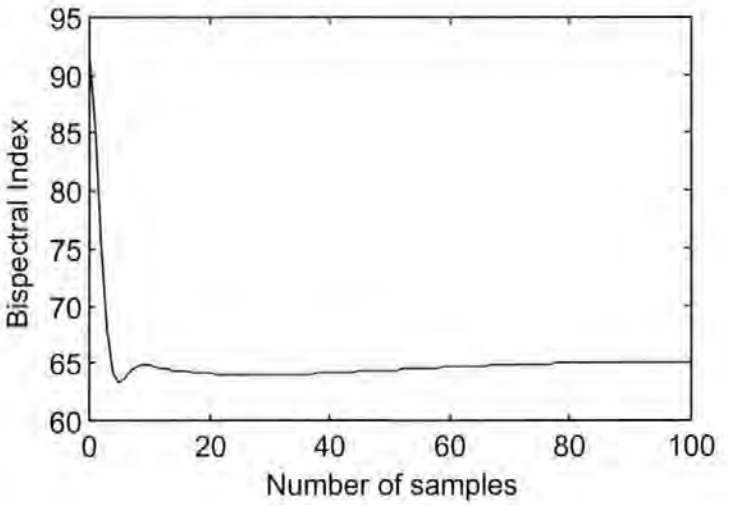


Figure 6-19 The response of the closed-loop PID control system to the BIS target of 65

6.5.5. Manual Adjustment

Using (6-17), the gains of the PID controller of the system in Figure 6-7 can be obtained from those of the system in Figure 6-8 as follows:

$k_{p1} = 17.05k_{p2} = 0.0066$, $k_{i1} = 17.05k_{i2} = 0.000063$ and $k_{d1} = 17.05k_{d2} = 0.4848$

The response of the system using above PID controller gains is shown in Figure 6-20.

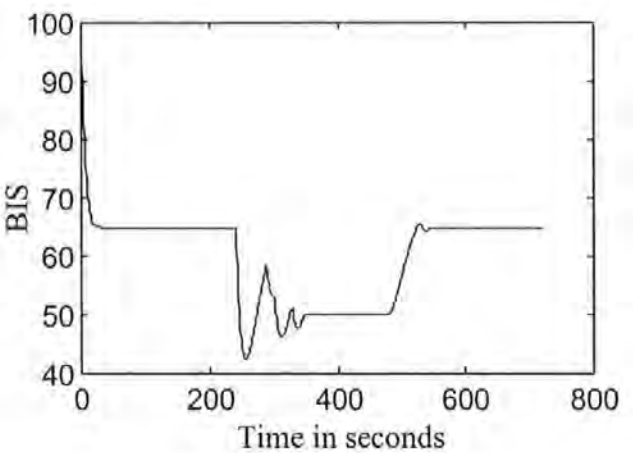


Figure 6-20 The BIS response of the closed-loop system to the BIS targets of 65, 50, and 65 ($K_p = 0.0066$, $K_i = 0.000063$, $K_d = 0.4848$)

Figure 6-20 shows that the step response of the system is excellent by the use of the designed controller gains. However, once the BIS target is changed, which always happens in a surgery, the initial system response is oscillatory and it takes a long time to be settled. This is because the gains were designed without taking the possible change in BIS target into consideration. Therefore a fine-tuning on the controller gains was performed manually using trial and error approach, and the following optimal gains were found:

$$k_p = 0.0024 \qquad k_i = 0.0000475 \qquad k_d = 0.365 \tag{6-23}$$

However, the controller gains in (6-23) are only optimal to the patients whose PK/PD parameters are identical to the PK/PD model used in the design, i.e. the reference model. These gains were used as the start point to tune the optimal gains for individual patients in Section 5.5.2.

Figure 6-21 shows the satisfactory system response when using the above optimal gains.

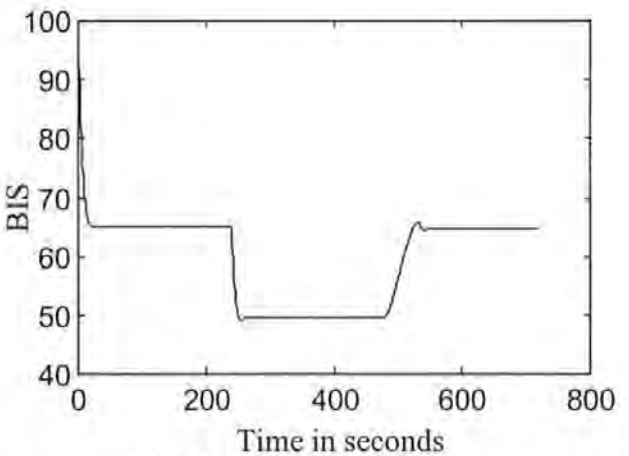


Figure 6-21 The BIS response of the closed-loop system to the BIS targets of 65, 50, and 65 ($K_p = 0.0024$, $K_i = 0.0000475$, $K_d = 0.365$)

6.6. System Control by Supervision

The CLAN system is assumed to be linear when developing its mathematical model. However a biomedical control system is safety critical, and a mechanism is needed to deal with any unknown non-linear dynamics. There are also some occasions where the infusion control needs to be supervised at a higher level, such as negative or maximal infusion rate, minimal or

maximal target drug concentration, change of BIS target etc. This is carried out at the system level to look after the CLAN system and make sure that the infusion is going well and the patient is safe. The system control unit is basically a central control and digital signal processing unit. The following sections describe how it works under various events.

6.6.1. Normal Operation

Under normal operation, the supervision system routinely performs the safety checks on infusion pump (and the second pump if two drugs are given) and the EEG monitor by reading their status. The pumps themselves could stop the infusion and enter into alarm status whenever they detect anything wrong with the pumps or the syringes. If this happens, the supervision system will issue an audio and visual warning signal, and automatically set up the pump communication again. If the alarm from the pump continues, physical intervention is required to clear the alarm. The supervision system can also identify whether the RS232 cables linking the PC and the pumps are disconnected or the power cables of the pumps and are disconnected.

Another routine safety check is on the EEG monitor. Since the data acquisition reads the raw EEG data and the processed EEG data in a block every five seconds from the buffers, an empty buffer indicates a RS232 cable disconnection or a persistent communication error for the last five seconds between the host PC and the monitor. Whenever such an error occurs the supervision system will launch an alarm along with an appropriate warning message displayed on the screen. If the buffers are not empty but the synchronization for either port is lost, an alarm and a warning message will also be given. The current data packet(s) will be treated as bad packet(s) and will be rejected and put into an error file.

The quality of Bispectral Index is monitored whenever a new BIS value becomes available. The new BIS value could be lost due to a loss of synchronisation or cable disconnection, or could be a fixed error value indicating that the EEG signal quality is bad and the monitor cannot produce a valid Bispectral Index for the current cycle. The new BIS value could also be incorrect due to a contaminated EEG signal, and this may happen when the impedance between the electrodes and the skin increases.

If the loss of the Bispectral Index is persistent, the supervision system will force the closed-loop control to be switched to open-loop control using the TCI control scheme until the problem is solved automatically or manually if necessary. As soon as the Bispectral Index is available again the closed-loop control will be enabled with the PID controller reset and

restarted.

Through statistical analysis of the clinical data obtained from the volunteer and patient studies, a mechanism has been developed to detect the contaminated Bispectral Index. Rates of change in Bispectral Index trend are used for this purpose. This mechanism is only used for removing the impulse noise from BIS trend.

The detection of impulse noise is based on the fact that the change of Bispectral Index is relatively smooth. From the result of statistical analysis on the clinical data, the rate of change (defined as db) below ±5 or the second order rate of change (defined as ddb) below ±0.8 are allowed otherwise an impulse noise is assumed. The quality of EEG signals has been taken into consideration for determining these values. This result implies that the maximum valid change in Bispectral Index in either direction is 25(e.g. 60, 85 or 60, 35) and the maximum oscillation in Bispectral Index is ±10(e.g. 55, 65, 55 or 55, 45, 55). The second order rate of change criterion is only used when two adjacent changes are in different direction (i.e. the occurrence of oscillation). In the clinical experiments on volunteers, the maximum db and ddb are 3.36 and 0.55 respectively. The db and ddb waveforms in the worst case with the 13th volunteer in propofol infusion study are shown in Figure 6-22 where the drug infusion started after 10 minutes baseline EEG recording. The maximum value of db was caused by the large overshoot that was the patient response to the initial bolus infusion.

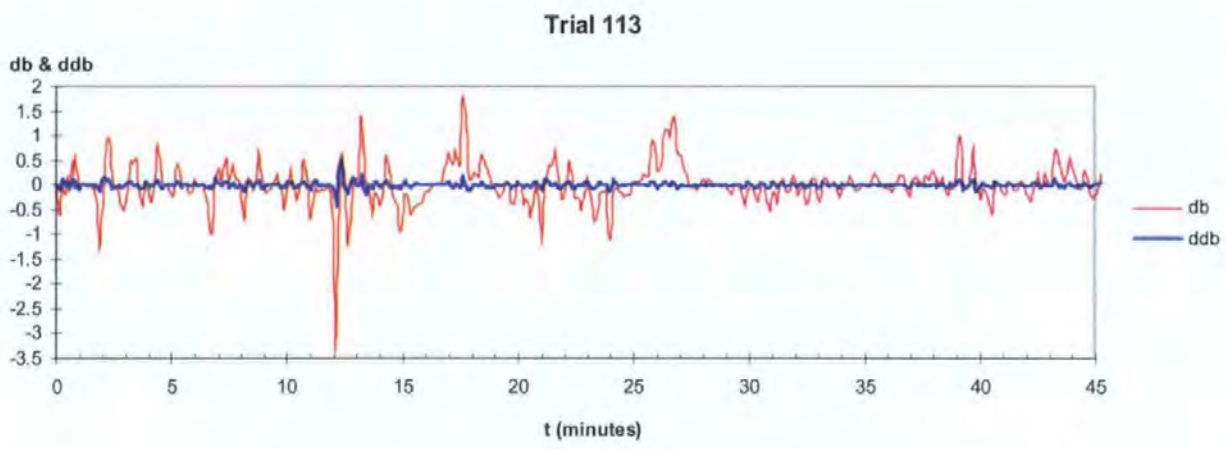


Figure 6-22 The rates of change in Bispectral Index in the worst case of clinical trial (where db(n) = [BIS(n)-BIS(n-1)]/Δt , ddb(n) = [db(n)-db(n-1)]/Δt , and Δt = 5 seconds)

6.6.2. Anaesthesia Induction

The anaesthesia induction is closed-loop controlled and starts with an initial bolus calculated from the target Bispectral Index, and then the CLAN system waits for the drug effect or BIS to reach its peak value. If the peak BIS value does not reach the target then another bolus will be given and this process will be repeated until the target BIS has been achieved. The peak BIS value is detected by performing a moving average on the current and part of the history of BIS values.

6.6.3. Anaesthesia Maintenance

As the PID controller only updates the TCI's target concentration, the infusion rate is calculated within TCI according to the site of target and the error between the target concentration and the estimated. However, which site for the TCI to target on is dependent on the BIS error.

During maintenance of anaesthesia, the Bispectral Index trend is relatively smooth, and the BIS error is usually small, and consequently the TCI targets on plasma to get the best control performance. Nevertheless, the effect site will become the site of target when the BIS error is large enough, and this would re-achieve the BIS target quickly. A threshold value for BIS error is used for controlling the target site. This value can be set for an individual subject at any time during the infusion depending on the pattern of the BIS trend in a certain period. The threshold value is normally within the BIS value range of 1~3 and is set to 2 by default according to computer simulation and clinical experience.

6.6.4. Response to Light Anaesthesia and Stimulation

Light anaesthesia usually occurs when the patient is stimulated physically or by environmental noises during surgery. Quick response from the CLAN system is required on these occasions.

BIS value will rise when the anaesthetic depth becomes lighter, which results in a big enough BIS error to force the TCI to target on effect site and consequently a bolus or a series of boluses will be given to re-achieve the target. The supervision system will monitor this process and stop the drug infusion when the BIS value is about to drop. This is because the drug effect will peak with hysteresis. Though the BIS error reaches an extreme value at the time the infusion is stopped, the error will begin to drop until the drug effect peaks. This way the CLAN system would reduce the overshoot to the minimum. Again, the rate of BIS change is used for the CLAN system to detect the peak BIS error.

6.6.5. Response to Overshoot and Undershoot

As can be seen in the clinical trials, the overshoot of Bispectral Index, either large or small, happens from time to time. However it is impossible to take the infused drug out of a patient, and the CLAN system will wait until the BIS value becomes close to the target. The infusion will be stopped and the PID controller will be disabled and reset when overshoot occurs. Because of the oscillatory nature of Bispectral Index, an overshoot threshold value for the BIS error is used to define the overshoot. This value is set by default to -2.5 according to clinical observation and statistical analysis and can be set for an individual subject at any infusion time.

The PID controller will be restarted when the Bispectral Index returns from an overshoot and becomes close to the target. It is too late to restart the drug infusion when the BIS error is zero due to the hysteresis, and therefore the overshoot threshold value in BIS error is used for resuming the infusion earlier and helping prevent big BIS jumps.

BIS prediction is another mechanism used by the CLAN system together with the overshoot threshold value to prevent sudden BIS jumps. The CLAN system monitors the first and second derivatives of the BIS change rate (i.e. the rate of BIS change and the rate of BIS error change) and uses the following prediction formula to predict the next BIS value:

$$BIS_{n+1} = BIS_n + e_n.T + a_n.T^2 \qquad \text{where } e_n = (BIS_n - BIS_{n-1})/T, \text{ and } a_n = (e_n - e_{n-1})/T$$

The first target concentration after the return from overshoot will be the estimated plasma drug concentration, and the first target site will be on plasma in order to achieve a smooth transition.

6.6.6. Emergency Handling

The supervision system monitors the performance of each hardware component in the closed loop system for any possible malfunction or failure, the quality of the Bispectral Index signal for any impulse noise, and the performance of the PID control. The CLAN system will automatically respond to any hardware and software failure or malfunction. If the failure or malfunction of the system is not recoverable, the infusion control will be automatically switched from closed-loop control to open-loop TCI control and the PID controller will get reset, and the target drug concentration will remain on the same value as the one at the time the closed-loop control stops. As soon as the system failure or malfunction disappears, the closed-loop control comes back into operation.

6.7. *Interactive User Interface*

An interactive user interface is implemented for the user to input patient information and set the runtime conditions (e.g., target of Bispectral Index, target concentration, maximum target concentration, etc.) before and during running the control system. While the system is running, the interactive user interface allows the user to control externally the system via various commands shown on the screen. It also allows making comments for any clinical events occurred at runtime, and all events recorded are accessible at runtime.

The interactive user interface provides an information rich screen display which includes the states of pumps and EEG monitor, current infusion rate, target Bispectral Index and target concentration, measured Bispectral Index and estimated plasma and effect site concentrations. See Appendix E for details. It also provides an efficient way to externally control the system either for normal operation or for emergency handling. It provides the commands to start, pause, and restart the drug infusion, and to change syringe and resume infusion. It allows the run-time modification of a number of system parameters that include target BIS, target concentration, PID controller gains (k_p, k_i, k_d), maximum target concentration (plasma or effect site), and the threshold BIS errors. Also the user can manually switch between closed-loop control and open-loop control if needed. Please refer to the Appendix E for a complete list of the available external commands.

6.8. *Test of Closed-loop Anaesthesia System*

6.8.1. Test of System on Patient Safety

In the design and implementation of a biological automatic control system, safety considerations are essential otherwise the control system would result in unpredictable or even disastrous consequences. Before the use of such a system, the possible sources of error should be anticipated so that the errors could be avoided or corrected automatically.

In a closed-loop control system, errors may arise from both software and hardware. The possible software errors may include programming errors, unreasonable or even wrong actions of control algorithm, communication errors, limited infusion pump precision. On the hardware side, the possible errors might arise from the disconnection of power cable from the pumps or monitor, the disconnection of the RS232 serial communication cables, and the disconnection of the electrode leads and IV line. Also the improper positioning of the syringe will cause infusion problem. The programming errors are bugs in the code, and the control algorithm associated errors may be the errors caused by the non-linear dose-response

relationship that could be seen from time to time in the clinical practices and experiments. Errors could also occur due to the inherent limitation of the algorithm, while communication errors are those generated by noise over the RS232 cables. Figure 6-23 summarizes the sources and the types of the possible errors.

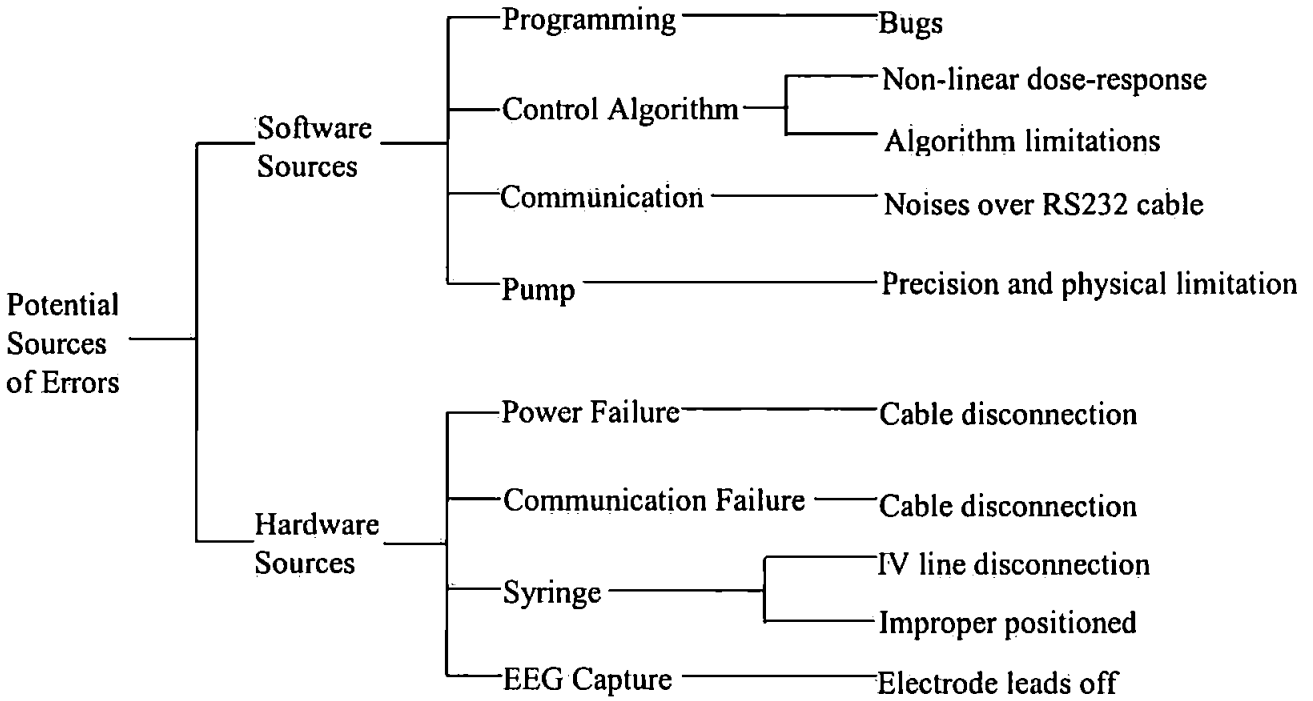


Figure 6-23 Possible sources and types of errors in the CLAN system

Generally, software errors could be avoided by careful coding of the system, or identified and automatically corrected by the system. However for the hardware errors, the system could only give either audio or visual warnings, manual interventions by the user are required. It is essential for a medical control system to be able to correct automatically the software errors if any, identify the hardware errors, give both audio and visual warning signals to the user, and take proper action before the errors cause problem.

In the CLAN system, all hardware errors have been deliberately generated, and the CLAN system is able to give appropriate warnings and take proper actions.

6.8.2. Test of System on Virtual Patients

As the PID controller is not an adaptive controller that is capable of adjusting the gains itself to adapt to the dynamic controlled object, a single set of controller gains are needed for all patients. This universal gain set could be generated in many ways, the only principle for

obtaining such gains is that an acceptable control performance must be guaranteed by those gains on the whole population under study. A possible method to do this is to average the gains available. The *AverageGain* set is therefore obtained by averaging the *kp*, *ki*, and *kd* columns in Table 5-1, the original optimal gains for the nine patients are re-listed together with the *AverageGain* in Table 6-6, where Patient1~Patient9 are defined in Table 4-5.

Table 6-6 Population average PID controller gains

	k_p	k_i	k_d
Patient 1	0.0024	0.000022	0.34
Patient 2	0.0015	0.000008	0.1
Patient 3	0.0012	0.00009	0.1
Patient 4	0.0012	0.00001	0.125
Patient 5	0.0024	0.00005	0.18
Patient 6	0.0024	0.00001	0.18
Patient 7	0.0019	0.00001	0.1
Patient 8	0.0024	0.00002	0.29
Patient 9	0.0008	0.00009	0.11
AverageGain	0.0018	0.000034	0.169

The effect site drug concentrations in these nine virtual patients are shown in Figure 6-24 with average gains used in the CLAN system, and the Bispectral Indexes are shown in Figure 6-25.

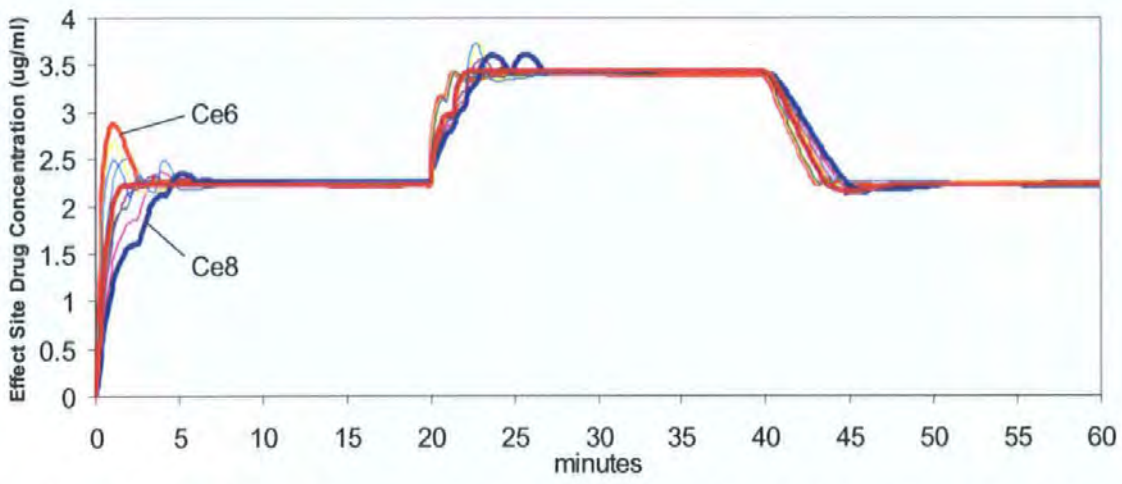


Figure 6-24 Effect site drug concentrations in the nine patients controlled by the CLAN system using *average gains* (Ce6, Ce8: effect site drug concentration in Patient6 and Patient8)

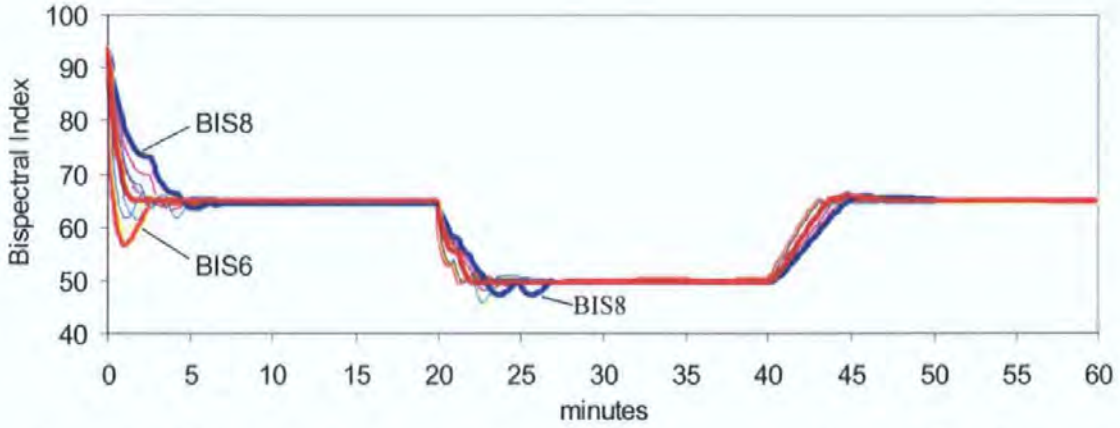


Figure 6-25 Bispectral Indexes in the nine patients controlled by the CLAN system using *average gains* (BIS6, BIS8: Bispectral Index in Patient6 and Patient8)

To do a robust test on the prototype CLAN system before using it in any clinical environments, the 78125 simulated patients defined in Table 4-7 are used with the average PID controller gains. To avoid running out of memory because of the huge amount of data to be generated, these 78125 hypothetical patients are equally divided into 5 main groups, each of which consists of 5 sub-groups. Therefore the whole test consists of 25 sub-tests, and each sub-test tests 3125 hypothetical patients in one go.

Each main group contains 15625 patients having identical central compartment volume, and each sub-group containing 3125 patients whose drug effect peak time are the same. The patients within each sub-group therefore have identical peak time value and central compartment volume with different permutation in the 5 rate constants.

To avoid redundant information, only the time evolution of the Bispectral Index of the patients is presented here because of the assumed linear relationship between the effect site drug concentration and the Bispectral Index. Figure 6-26, Figure 6-27, and Figure 6-28 show the simulation results on the patients in three of the five main groups (46895 patients), respectively. These hypothetical patients have either the maximal or mean or the minimal central compartment volumes defined in Table 4-7. The means and standard deviations of Bispectral Index in a main group (Vc=16.9 litres) are presented in Table 6-7.

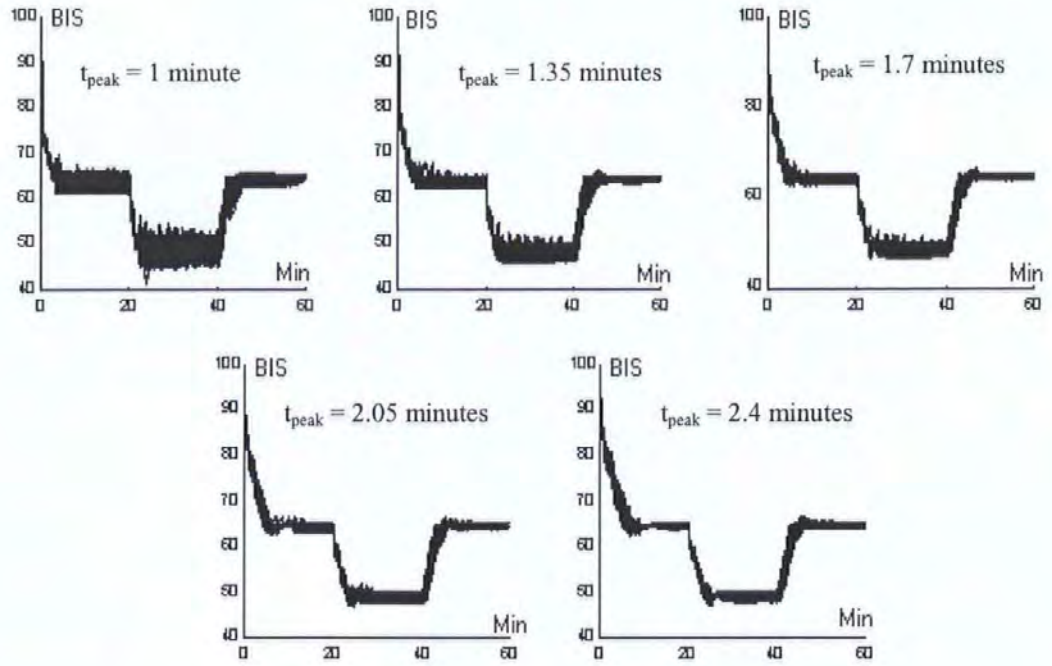


Figure 6-26 Simulation result on 15625 patients with central compartment volume of 16.9 litres (t_{peak}: drug effect peak time; each of the 5 figures presents the result on 3125 patients)

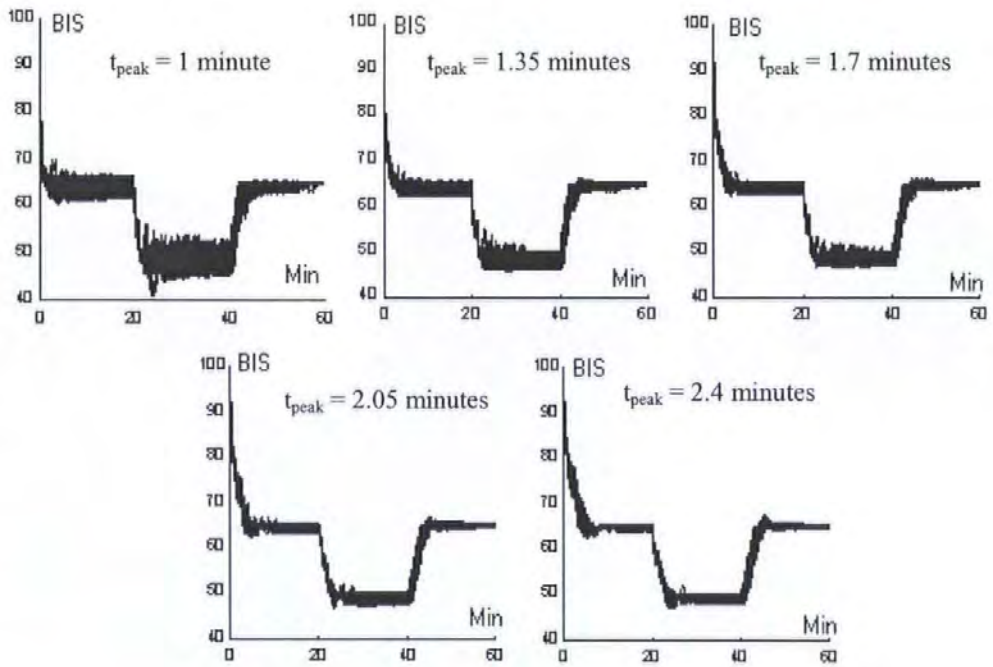


Figure 6-27 Simulation result on 15625 patients with central compartment volume of 13.6 litres (tpeak: drug effect peak time; each of the 5 figures presents the result on 3125 patients)

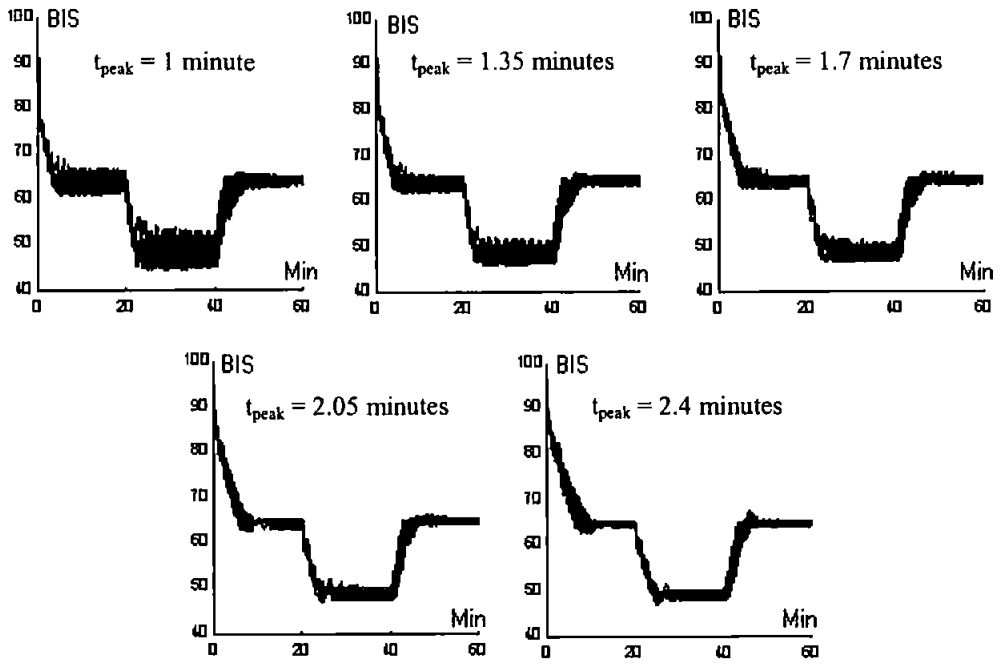


Figure 6-28 Simulation result on 15625 patients with central compartment volume of 20.2 litres (tpeak: drug effect peak time; each of the 5 figures presents the result on 3125 patients)

The patients associated with Figure 6-26 have the mean central compartment volume of 16.9 litres, and those associated with Figure 6-27 have the minimal volume of 13.6 litres, while those associated with Figure 6-28 have the maximal volume of 20.2 litres.

Table 6-7 Mean and standard deviation of Bispectral Index of a patient group (Vc = 16.9 litres)

	BIS Target	Sub-group1 t_{peak}=1 min	Sub-group2 t_{peak}=1.35 min	Sub-group3 t_{peak}=1.7 min	Sub-group4 t_{peak}=2.05 min	Sub-group5 t_{peak}=2.4 min
No. of patients	-	3125	3125	3125	3125	3125
10~20 minutes	65	64.43±0.98	64.76±0.37	64.73±0.34	64.73±0.32	64.74±0.30
30~40 minutes	50	49.21±1.33	49.80±0.40	49.75±0.39	49.75±0.36	49.75±0.35
50~60 minutes	65	64.77±0.25	64.80±0.25	64.81±0.25	64.79±0.25	64.74±0.24

The control performance of the CLAN system on the other two main groups of the patients falls either between those shown in Figure 6-26 and Figure 6-27 for the group having the volume of 15.3 litres, or between those shown in Figure 6-26 and Figure 6-28 for the group having the volume of 18.5 litres.

6.9. Discussion and Conclusion

All components in the CLAN system shown in Figure 4-1 have been designed and implemented. The software components are written in C language. The design has met the desired specifications. The prototype of the CLAN system is tested on a population of hypothetical patients. Though the Bispectral Indexes from the patients do not converge to a single value in this robust test, the control performance is as expected and the performance is acceptable.

Though the CLAN system designed and implemented is specifically for controlling the infusion of hypnotic propofol and analgesic alfentanil, it supports the delivering of other analgesics by selecting them in the command file. However, the PID controller gains have to be redesigned with an appropriate pharmacodynamic model so that the CLAN system can be used for delivering other hypnotics with closed-loop control. Some other anaesthesia pumps such as Harvard and I-Med are also supported by the CLAN system.

The result of the simulation study on the 78125 patients demonstrates that the designed CLAN system is capable of achieving, tracking, and maintaining dynamic Bispectral Index targets in a population with a broad range of PK/PD parameter values.

7. Evaluation of the Closed-Loop Anaesthesia (CLAN) System

7.1. Introduction

Automated control systems have widespread application in critical applications. However, their use in medical care is relatively unusual. After intensive simulations on the virtual patients and appropriate electrical testing the closed-loop system was evaluated in volunteers and patients. Each clinical study was approved by the Ethical Committee and all subjects gave consent in writing. Considerable attention was given to electrical safety for the entire apparatus. An isolation transformer is used for providing the power supply for all equipment, and formal electrical checking is carried out on individual items of the complete assembled system.

Initial testing took place on volunteers. This allowed complete control over the experimental protocol without impingement of clinical (surgical) factors. Nevertheless, safety of volunteers is paramount and this was reflected in the staffing, general equipment and location.

After testing of the CLAN system on volunteers with physical stimulation or N_2O inhalation, it was further tested on patients undergoing knee surgery with epidural, and finally on patients undergoing back surgery with alfentanil for total intravenous anaesthesia delivery.

7.2. Safety Test of CLAN System

The real time safety tests have been done on the CLAN system when running in simulation mode. The ability of hardware malfunction identification and if possible correction were tested with the running of two Graseby 3400 pumps and the Aspect A-1000 EEG monitor.

In these tests, error conditions were deliberately created, and then fixed thereafter. The following is a list of the tests that have been done.

- Disconnecting/Re-connecting each of the three RS232 cables from computer, Graseby 3400 pumps, or the A-1000 EEG monitor.
- Disconnecting/Re-connecting the power cables of the pumps and EEG monitor
- Creating/Fixing error from seating the syringes

The CLAN system responded to the deliberately created errors by giving appropriate visual and audio warning messages, and as soon as the error condition disappeared, the CLAN

system was able to resume correctly. If the problem was from the pumps or syringes, then the pumps would be re-initialised and the infused volume would be set to those before the error condition had arisen.

7.3. General Methods

Volunteer experiments took place in the "anaesthetic room" of a standard NHS operating theatre. In addition to the research engineer, a qualified anaesthetist (typically more than one) and a trained anaesthetic assistant were present. All experiments with the CLAN system were fully controlled by the medical staff, and the role of the research engineer was limited to supervising the operation of the software, input of data required by the experiments and offering technical advice.

The "anaesthetic room" is a standard clinical environment including all necessary and routine equipment. "Standard" monitoring was applied to all volunteers/patients including non-invasive blood pressure, pulse-oximetry and ECG. The experimental area was fully enclosed and "Do not disturb" signs were placed on the external doors. Volunteers wore standard cotton "theatre greens", patients wore "theatre gowns" and all lay on a standard operating theatre trolley. A full range of routine and emergency drugs, and clinical equipment was immediately to hand. Use of a written checklist ensured a thorough preparation of all relevant items.

For all subjects of the four clinical studies, five electrodes were attached to the forehead of subjects to obtain two channel (bipolar, Fp1(+), F7(-), Fpz(ground), and Fp2(+), F8(-), international 10-20 system electrode placement chart) EEG signals. The impedance between any electrode and the skin was maintained below 10kΩ (usually less than 5 kΩ) to guarantee the quality of the EEG signals.

Every 5 seconds a Bispectral Index and some power spectral variables were calculated from the EEG signals by a built-in proprietary algorithm (BIS V3.12 for the first three studies, BIS V3.30 for the fourth study) installed in the Aspect A-1000 EEG monitor, the raw EEG signals containing artefacts were set to be rejected from these calculations. Throughout each experiment, the two channel raw EEG signals, BIS and all the other derived EEG variables were recorded by the CLAN system. BIS and some other EEG variables (including total power, SEF, MF, etc.) were displayed on the screen in real-time. Blood pressure and heart rate were also monitored in accordance with normal clinical practice. The full list of the A-1000 EEG monitor settings for all subjects is given in Appendix D.

To take full advantage of the computer processor speed, the CLAN system ran in pure DOS mode on a 120MHz Compaq personal computer with the A-1000 EEG monitor and the Graseby 3400 anaesthesia pump(s) connected via RS232 interfaces. The control scheme and the population average PID controller gains, which were used in the simulations on 78125 virtual patients, were used for all cases of the four studies. Other dynamic configurations of the CLAN system are listed in Appendix C.

For the purpose of statistical analysis on the clinical data obtained from the experiments, induction time is defined as the time spent by the CLAN system from start of infusion until the BIS value reaches target or below BIS_T. (1+4%) if then the BIS trend becomes stable, here BIS_T is the BIS target. BIS stable time is defined as the time from start of infusion to the time from which the BIS trend is persistently within BIS_T. (1±4%). Recovery time is defined as the time from the termination of infusion to the time the patients woke up. Since the times at which the patients opened their eyes were not recorded for all patients, for those the eye-open times were not recorded, the recovery time is defined from the termination of infusion until BIS value reaches 90 according to other reports (Epstein, 1998; Baker, Sleigh and Smith, 2000) and our own clinical observation. Finally, the predicted wakening concentration is the predicted effect site propofol concentration when patients woke up or BIS reached 90 after the termination of infusion.

Above methods and definitions apply to all clinical studies.

7.4. Propofol Sedation on Volunteers

7.4.1. Objective

The CLAN system was first tested on volunteers for propofol sedation. The objective of this study is to test the performance of the CLAN system on controlling the level of sedation in human subjects with or without external stimulation but without interference from an analgesic agent.

7.4.2. Methods

For all subjects in this study, no premedication was given before the experiments. The target Bispectral Index was set to 65 to achieve hypnotic effect(Baker, Sleigh and Smith, 2000) in the volunteers, and the experiment protocol for this study is shown in Figure 7-1 that includes 5 periods.

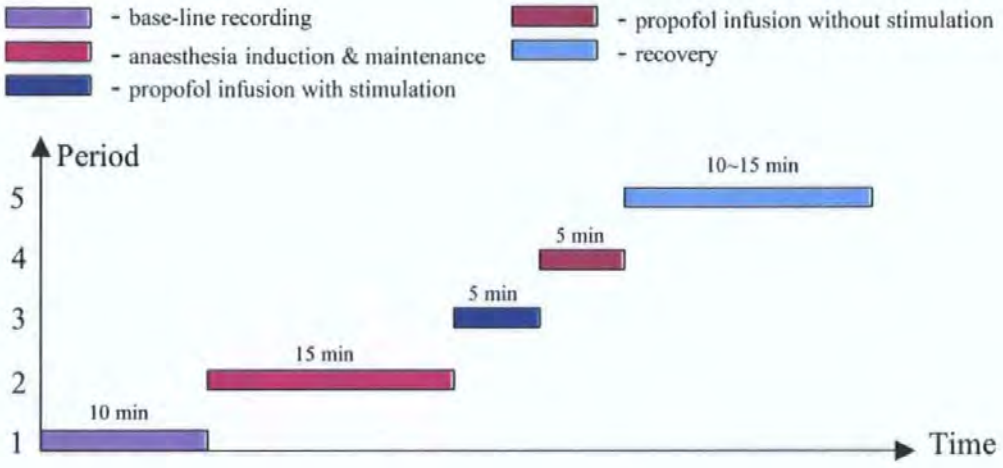


Figure 7-1 Experiment protocol for volunteer study with propofol and stimulation

With regard to the time length for each of the 5 periods, there is a trade-off between the perfect science and practicality/safety in a clinical experiment involving human beings. The lengths of experiment periods above were chosen on practical considerations and clinical experience from a senior anaesthetist, which was likely to allow proper equilibration of the subject in each of the experimental conditions whilst giving an overall experimental "envelop" which was practicable.

Five minutes stimulation was given during the maintenance period of anaesthesia by a nerve stimulator applied to the wrist with an electrical current of 30mA during the first two minutes increased to 40mA during the other three minutes of the stimulation.

7.4.3. Results

Thirteen fit volunteers (ASA I&II, 23-57 years, 56-92kg, 8 men and 5 women) entered into this study. The experiment protocol was completed in 12 volunteers with satisfactory results from 11 of them. The characteristics of the 13 volunteers are listed in Table 7-1.

Table 7-1 Characteristics of the volunteers for propofol sedation

Volunteer	1	2	3	4	5	6	7	8	9	10	11	12	13	Mean (SD)
Gender	M	F	M	M	M	M	F	F	M	M	M	F	M	
Age (years)	30	31	23	40	29	57	29	35	28	39	31	40	29	33.9 (8.6)
Weight (kg)	74	72	76	73	80	90	57	56	80	92	64	80	80	74.9 (10.9)
Height (cm)	180	160	183	175	175	183	157	168	175	186	174	180	183	175.3 (8.9)

The protocol was not completed in the first subject due to long-lasting absence of BIS value from the EEG monitor and the propofol infusion was then manually switched to TCI control. The clinical data obtained from this volunteer is therefore excluded from the statistical analysis. The failure was caused by bad contact between the electrodes and skin when the subject moved, which in return caused a high impedance (over 10,000 ohm with 2,000 ohm recommended) between the brain signal and the external signal amplifier of the EEG monitor.

The experiment protocol defined previously in Figure 7-1 was not exactly followed due to various unavoidable reasons including hospital staff temporary availability and equipments malfunction. The actual protocols performed in volunteers are shown in Figure 7-2. Generally, the experiment protocol was changed in volunteers 1, 3-5, 9, and 11. Subject 3 was not given stimulation at all because the desired BIS target was never achieved. For the 4th subject, there was a large overshoot (BIS4 in Figure 7-3) during the sedation induction, and the stimulation was not given until the BIS returned to around the BIS target at a time 25 minutes after the start of infusion, and infusion stopped immediately after stimulation on this subject. Pump failures (all caused by subject's body movement) forced 11 minutes delay in giving stimulation to the 5th volunteer. The stimulation to the 9th subject was given 5 minutes before the schedule due to the earlier stabilisation of Bispectral Index in this subject. The infusion started 3 minutes after the schedule in subject 11 because of a problem of syringe seating.

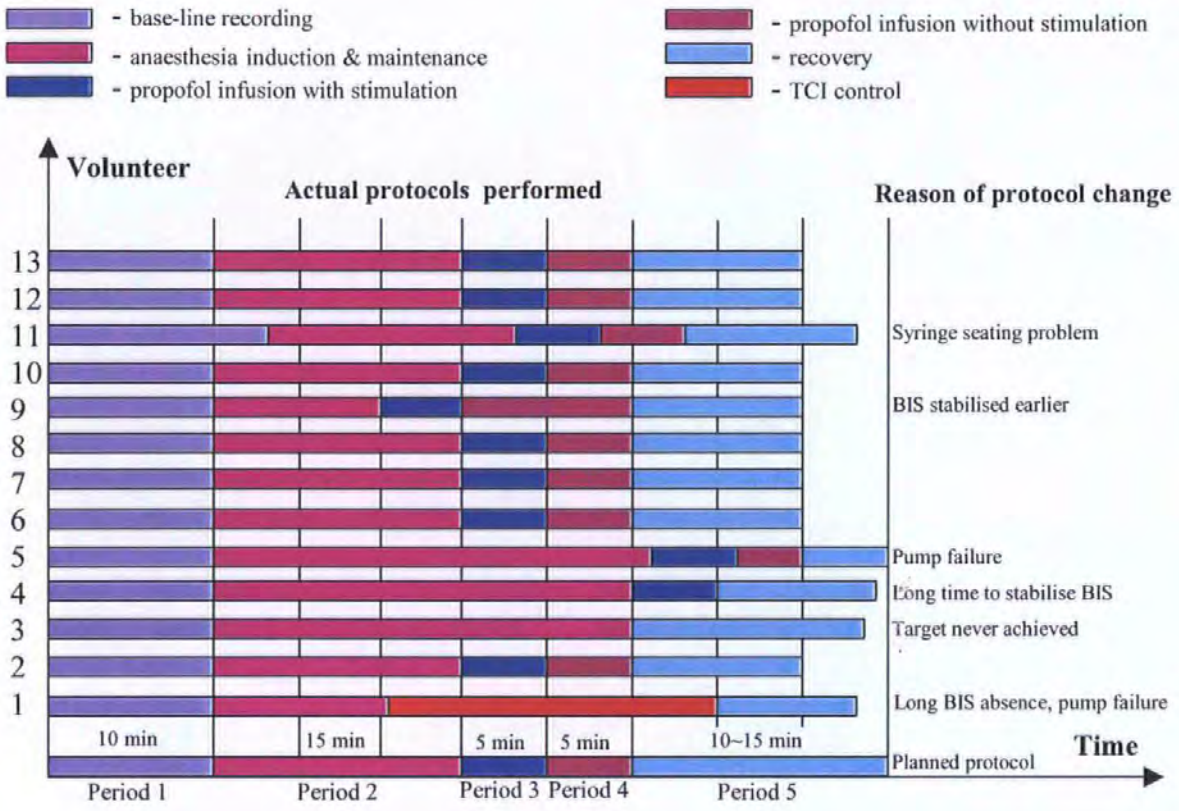


Figure 7-2 Actual experiment protocols performed in volunteers (bottom - planned protocol)

The measured Bispectral Index (BIS_i for the i^{th} volunteer) and the predicted propofol concentration in plasma (Cp_i for the i^{th} volunteer) and at effect site (Ce_i for the i^{th} volunteer) are presented in Figure 7-3, Figure 7-4, Figure 7-6, Figure 7-7, and Figure 7-8, respectively. Figure 7-5 is the combined figure of Figure 7-3 and Figure 7-4 but normalised to the stimulation time. The lower the BIS value, the deeper in depth of anaesthesia. The *x* axis shows the time in minutes after the start of infusion in all figures except for the Figure 7-5 where the x axis shows the time after the start of stimulation.

The data on predicted plasma and effect site drug concentration estimated by the reference model were never archived by human mistake in the experiment with the fourth subject. Before the experiment with the 8^{th} volunteer, the CLAN system was designed to automatically stop archiving the predicted concentrations after the termination of infusion. Therefore, the predicted concentrations during recovery period are not available from the first volunteer to the 7^{th} volunteer.

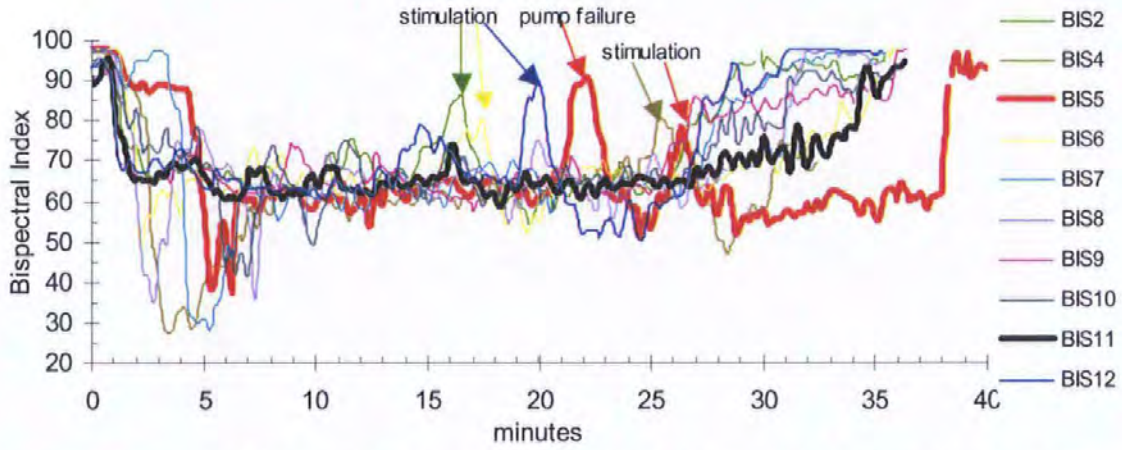


Figure 7-3 Expected BIS trends in 10 volunteers (BIS*i*: Bispectral Index in the *i*th volunteer)

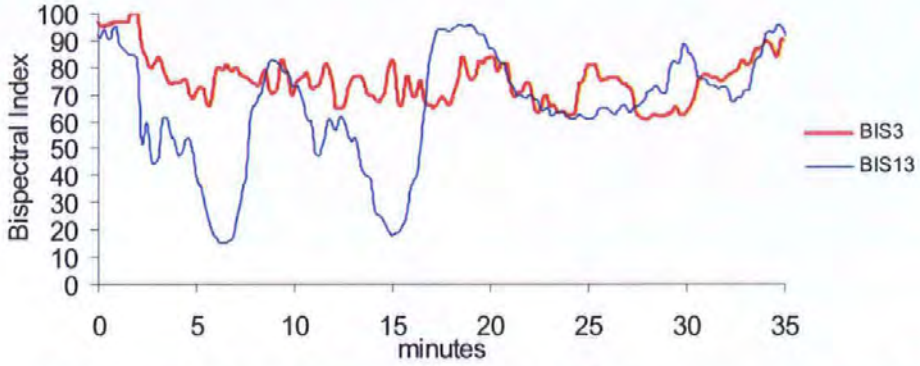


Figure 7-4 Unexpected BIS trends in the 3rd and 13th volunteers in propofol sedation study

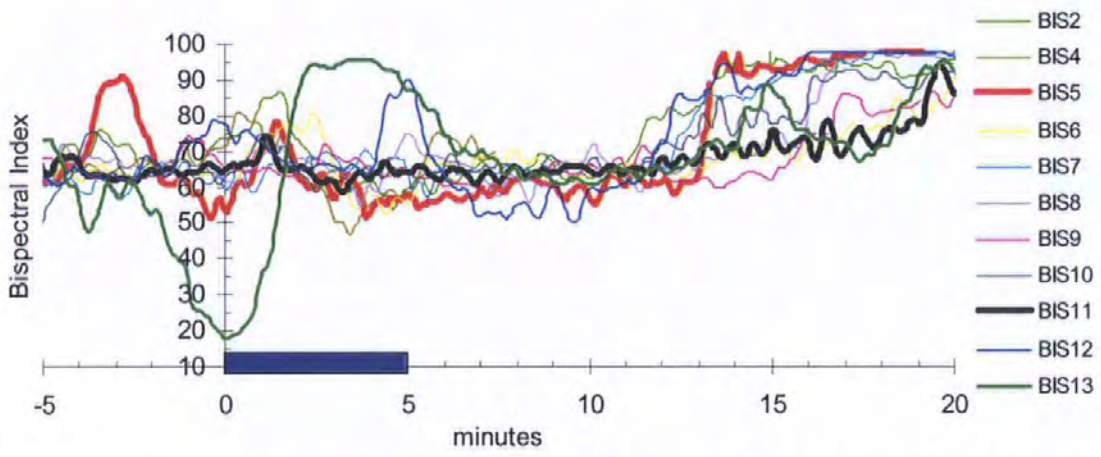


Figure 7-5 The BIS trends in 11 volunteers normalised by stimulation time indicated by the blue bar

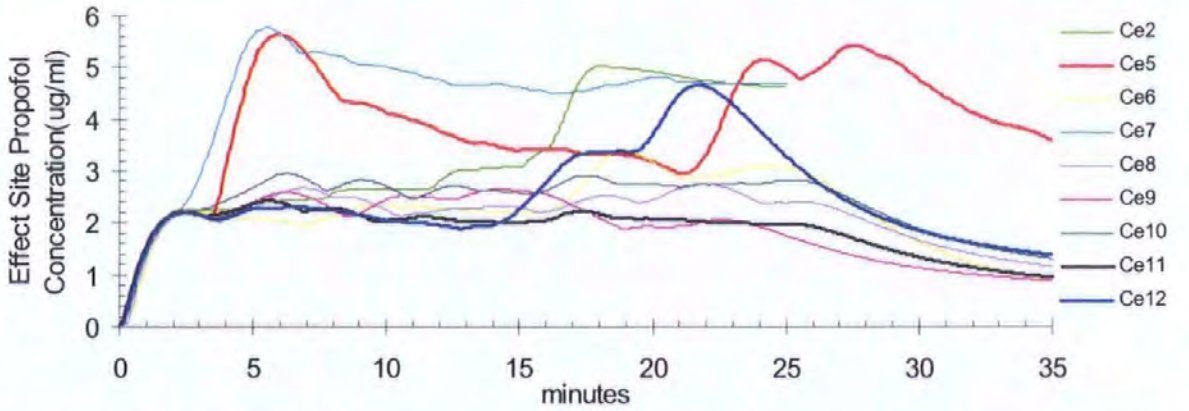


Figure 7-6 Predicted effect site propofol concentration of 9 volunteers in propofol sedation (Ce*i*: predicted concentration in volunteer *i*, data lost in the 4th volunteer)

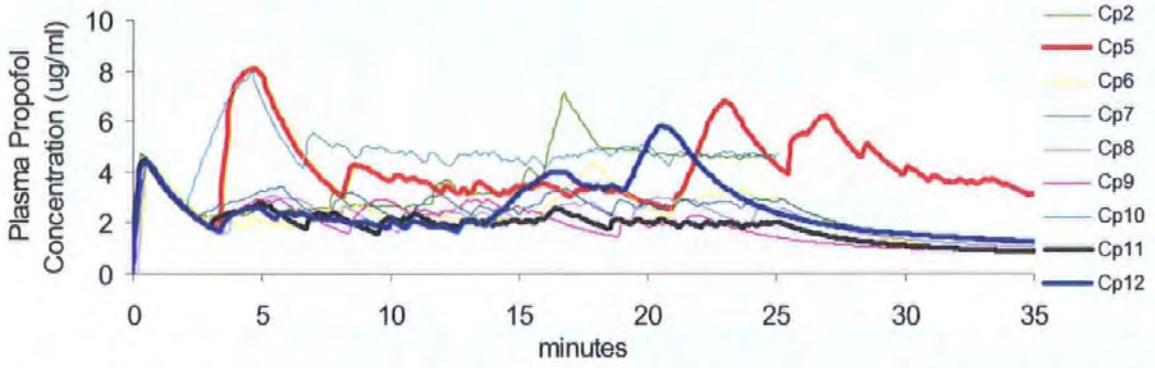


Figure 7-7 Predicted plasma propofol concentration of 9 volunteers in propofol sedation (Cp*i*: predicted concentration in volunteer *i*, data lost in the 4th volunteer)

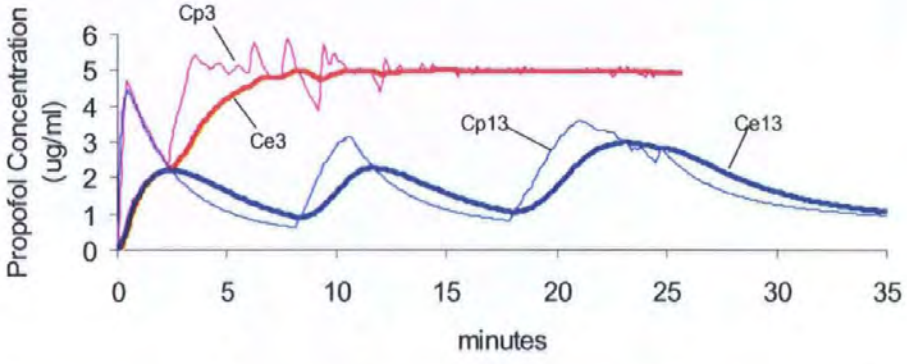


Figure 7-8 Predicted propofol concentration in plasma and at effect site in the 3rd (Cp3, Ce3) and 13th (Cp13, Ce13) volunteers

The induction time, BIS stable time, recovery time, and predicted wakening concentration (see Section 7.3 for definitions) in individual volunteers are listed in Table 7-2. The 3rd subject is omitted from these statistics because the BIS target was never achieved in this subject.

Generally, the CLAN system achieved the BIS target in the 12 subjects in 3.2(1.4) minutes and successfully stabilises the BIS trends in 7.2(6.0) minutes after the start of infusion. While 6.4(2.4) minutes after the end of infusion, the predicted effect site concentration or predicted wakening concentration was 1.3(0.4) mcg/ml, and the BIS values measured in the subjects reached 90 at which 3 subjects opened their eyes, and 5 of them became responsive to audio stimulation, however no records were made on the others.

Table 7-2 Induction time, BIS stable time, recovery time, and predicted wakening concentration for the 12 volunteers in propofol sedation study

	Volunteer												Mean
	2	3	4	5	6	7	8	9	10	11	12	13	(SD)
Induction Time (min)	2.6	N/A	2.7	5.0	2.2	4.2	2.1	1.7	5.7	1.9	4.8	2.2	3.2 (1.4)
BIS Stable Time (min)	2.6	N/A	8.4	6.8	4.2	6.7	7.9	1.7	12.1	1.9	4.8	22.6	7.2 (6.0)
Recovery Time (min)	3.5	N/A	6.0	3.5	10	5.2	6.5	7.3	6.1	9.4	3.5	9.1	6.4 (2.4)
Wakening concentration*	N/A	N/A	N/A	N/A	0.9	N/A	1.5	1.1	1.7	1.0	2.1	1.1	1.3 (0.4)

*effect site concentration in mcg/ml

In response to the same dose (in mg/kg) of initial bolus during the induction of sedation, the Bispectral Indexes in four volunteers (volunteers 2, 9, 11, and 12) were successfully brought to the target, overshoot can be seen in four volunteers (minimal BIS value of 28.1, 45.3, 35.9, and 15.6 in volunteers 4, 6, 8 and 13, respectively), whereas undershoot occurred in the other four (volunteers 3, 5, 7, and 10). Overshoot or undershoot after the anaesthesia induction

bolus infusion is expected in subjects because of inter-patient variability.

To achieve the BIS target in the four volunteers with undershoot, more drug was infused by the CLAN system when BIS value was above the target indicating a lighter anaesthesia. This was associated with the rise in predicted propofol concentration (by the reference model) both in plasma instantly and at effect site with hysteresis (see Figure 7-6 and Figure 7-7). Three of these four volunteers (subject 5, 7, and 10) developed overshoot (39.5, 39, and 41.8 in BIS, respectively) because of this extra drug, whereas the amount of drug infused was still not enough to achieve the BIS target in the other volunteer or subject 3.

After a stable BIS was maintained (except for the 13th volunteer), a five-minutes long painful stimulation was given to volunteers. All volunteers physically responded to the stimulation (peripheral nerve stimulator at the wrist with electrical current of 30mA for 2 minutes followed by 40mA for 3 minutes), which indicated that anaesthesia became light because of the stimulation. A significant BIS rise was expected after the physical stimulation. The BIS values of the 10 volunteers rose in response to the stimulation though the time to start responding varies in subjects. The CLAN system at the same time infused more drug into the volunteers in order to bring the BIS values back to the target, the more the BIS value rose in a subject, the more drug was given. Some volunteers developed overshoot (e.g., volunteer 12) and some did not. The BIS target was achieved again during or after the stimulation depending on the PK/PD characteristics of individual subjects. After the infusion had stopped, the recovery was quick (minimum of 3.5 minutes) in some subjects but slow (up to10 minutes) in others. This depends on the drug elimination rate of individual subjects.

The BIS target was never achieved in the third volunteer in whom the maximal predicted drug concentration safety limit (5 mcg/ml) was hit, which expectedly prevented this subject from being given enough drug to achieve the target while the measured BIS was below the target. While in the experiment with the thirteenth volunteer, the BIS value was stabilised after 22.6 minutes. Figure 7-4 and Figure 7-8 show the measured Bispectral Index, predicted propofol concentrations in plasma and at effect site of the third and the thirteenth volunteers. Table 7-3 gives the means and standard deviations of BIS values during the maintenance period (after anaesthesia induction as defined in induction time) before (Period 2) and after (Period 4) the stimulation and those during (Period 3) the stimulation period. It also gives the overall mean and standard deviation on all 12 subjects during each of the three periods (63.1(8.2), 66.1(11.4), and 63.8(5.3) for those before, during, and after the stimulation, respectively). There is no data for volunteer 4 during the Period 3 as the infusion was terminated

immediately after the stimulation period (see Figure 7-2) due to the infusion time length limitation for the experiment protocol. After anaesthesia induction, the BIS target was best maintained before and after the stimulation (Period 2, 4) but worst maintained during the stimulation (Period 3). This is because BIS usually rises during or after stimulation (indicated by the arrows in Figure 7-3) as expected, which increases the deviation. The overall control performance of the CLAN system can be represented by the mean and standard deviation Mean(SD) on all data during the three periods in all 12 volunteers: 63.9±8.7. The last column of this table shows the mean (SD) values excluding the subject 13, which gives the overall performance of 64.5 (4.9).

Table 7-3 The Mean(SD) values of BIS in volunteers in propofol sedation study

	Volunteers													
	2	3	4	5	6	7	8	9	10	11	12	13	All	All*
Period 2**	67.5 (2.9)	N/A	62.6 (3.0)	62.2 (2.5)	64.9 (2.6)	62.2 (2.6)	64.9 (3.0)	66.2 (3.1)	63.5 (1.3)	64.8 (2.6)	66.2 (4.1)	49.8 (19.0)	63.1 (8.2)	64.6 (3.5)
Period 3	68.8 (9.9)	N/A	63.3 (10.3)	62.0 (6.8)	66.3 (9.0)	66.0 (3.0)	65.4 (4.5)	62.5 (2.0)	65.3 (3.8)	64.9 (3.2)	70.9 (7.2)	71.5 (30.1)	66.1 (11.4)	65.5 (7.1)
Period 4	63.4 (2.6)	N/A	N/A	58.6 (2.2)	65.5 (2.9)	64.0 (2.0)	64.8 (4.3)	64.0 (2.9)	65.4 (1.7)	64.1 (1.4)	59.1 (9.5)	68.6 (7.8)	63.8 (5.3)	63.2 (4.7)
All Periods	66.9 (5.6)	N/A	62.7 (5.6)	61.4 (4.0)	65.4 (5.0)	63.7 (3.0)	65.0 (3.9)	64.9 (3.2)	64.9 (2.8)	64.7 (2.5)	65.7 (7.4)	58.7 (22.8)	63.9 (8.7)	64.5 (4.9)

*all subjects excluding subject 13 **after anaesthesia induction

Table 7-4 shows the Mean (SD) values of the predicted effect site concentration during the three periods in 12 subjects. As explained previously, the predicted concentration in subject 4 was not archived. The Mean (SD) value of the predicted effect site concentration in subject 3 is calculated on the data from the time the predicted effect site concentration became stable (i.e., reached the maximal concentration safety limit of 5.0 mcg/ml) up to the end of infusion. The last column shows the mean (SD) values excluding subject 13.

Table 7-4 The Mean(SD) values of Ce in volunteers in propofol sedation study

	Volunteers													
	2	3	4	5	6	7	8	9	10	11	12	13	All	All*
Period 2**	2.6 (0.3)	N/A	N/A	3.8 (0.6)	2.2 (0.1)	5.0 (0.2)	2.3 (0.1)	2.4 (0.2)	2.7 (0.0)	2.2 (0.1)	2.1 (0.1)	1.7 (0.5)	2.6 (0.9)	2.8 (0.9)
Period 3	4.4 (0.7)	N/A	N/A	5.1 (0.2)	2.8 (0.5)	4.6 (0.1)	2.4 (0.1)	2.3 (0.3)	2.8 (0.1)	2.1 (0.1)	3.1 (0.4)	1.3 (0.2)	3.1 (1.2)	3.3 (1.1)
Period 4	4.7 (0.1)	N/A	N/A	4.1 (0.3)	3.0 (0.1)	4.7 (0.0)	2.6 (0.1)	2.0 (0.1)	2.7 (0.0)	2.0 (0.0)	4.2 (0.4)	2.7 (0.4)	3.3 (1.0)	3.3 (1.1)
All Periods	3.5 (1.1)	5.0 (0.1)	N/A	4.1 (0.7)	2.5 (0.4)	4.8 (0.2)	2.4 (0.2)	2.3 (0.3)	2.7 (0.1)	2.1 (0.1)	2.8 (0.9)	2.0 (0.8)	3.1 (1.2)	3.2 (1.1)

*all subjects excluding subject 13 **after anaesthesia induction

7.4.4. Discussion

The results from this study on the 13 volunteers show that the propofol infusion was well under control of the developed closed-loop anaesthesia or CLAN system except for the first and the last (or 13th) volunteers, and Bispectral Index was shown to be a good descriptor of sedation level.

The performance of the CLAN system on all subjects except for the 13th subject was clinically acceptable. Once the BIS was stabilised, the CLAN system was able to maintain stable state. The mean (SD) values of BIS in subject 2 to subject 12 during the three periods (Period 2 to Period 4) were 64.6(3.5), 65.5(7.1), and 63.2(4.7), respectively with a target BIS of 65. The overall performance during all three periods was 64.5(4.9). The best result was obtained from Period 2 after anaesthesia induction, whereas the worst result came from the stimulation period or Period 3. The CLAN system successfully re-stabilised the BIS during or after the stimulation and achieved the mean (SD) value of 63.2(4.7) in BIS after the stimulation. The ability of the CLAN system to re-achieve and re-stabilise the BIS during or after the stimulation meets the requirement in clinical practice.

Because of inter-subject variability, subjects were actually in different levels of sedation when the BIS was stably maintained at around 65. Any environment noises could awake those

subjects who were in lighter levels of sedation. This can be confirmed from some subjects in whom the BIS rose from the stable state during the maintenance phases (before or after the stimulation) while they were moving or talking. However, the CLAN system successfully re-achieved the BIS target within a short period of time.

BIS oscillation occurred in subject 10 and 13 before the BIS was stabilised in 12.1 minutes and 22.6 minutes, respectively. For subject 10, it seems the PID controller gains are not suitable for this volunteer. The BIS and predicted concentrations are redrawn and shown in Figure 7-9. The initial bolus did not achieve the BIS target in the subject. When the loop was closed at 2.8 minutes the CLAN system steadily gave drug to the subject. This process can be seen on the predicted plasma concentration Cp (thin line). However too much drug was given so that overshoot occurred, and this process repeated once more before the BIS was stabilised eventually in 12.1 minutes.

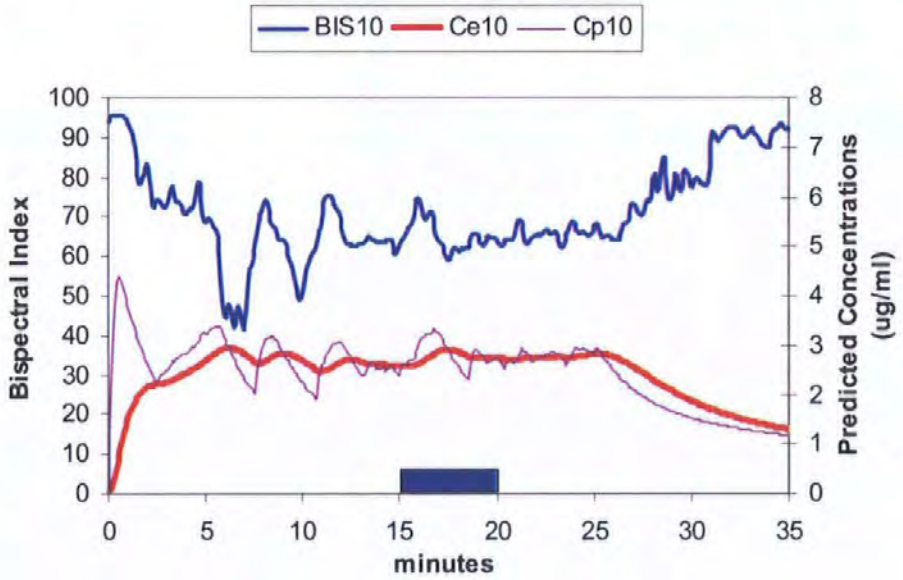


Figure 7-9 Bispectral Index (upper line) and Predicted concentrations in subject 10 (physical stimulation time is indicated by the blue bar)

Drug effect hysteresis and inappropriate PID controller gains could be two of the main reasons for the BIS oscillation in this subject.

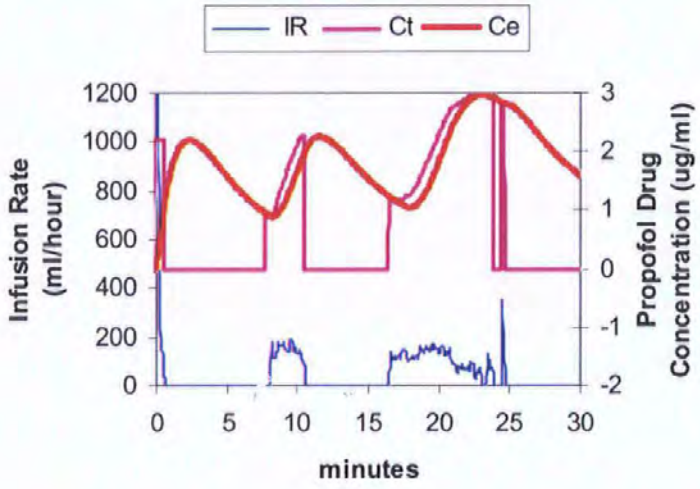
As explained in Chapter 2, hysteresis is the additional time needed for the drug concentration in the brain to rise and induce anaesthesia after the infusion of any amount of drug, it is also known as drug effect peak time or t_p. When the built-in PK model is targeting on effect site, it always gives such drug infusion rates so that the predicted effect site concentration would be the target concentration (generated by the PID controller) after the hysteresis. Consequently, more drug must be given to compensate the drug distribution loss during the hysteresis in order to achieve the target after it. This means that the predicted drug concentrations (Ce and Cp) will be inherently oscillatory if using this infusion rate generation scheme. In clinical practice, there is a need to achieve a desired anaesthesia level as quickly as possible. Therefore, this scheme is always used if undershoot occurs. When BIS is stable, however, the infusion scheme of targeting on plasma is used, which does not incorporate the hysteresis effect and so provides smooth predicted concentrations. This scheme takes longer time to achieve the desired target if used when an undershoot occurs.

On the other hand, the PID controller in nature tends to be oscillatory at the beginning of achieving a target since the gains were not tuned to a specific patient. Although the PID controller has been tuned to minimise this oscillation and made a trade-off between the oscillation and response speed for the patients described in Chapter 5, it is only optimal for the patients with population average pharmacokinetic and pharmacodynamic parameters.

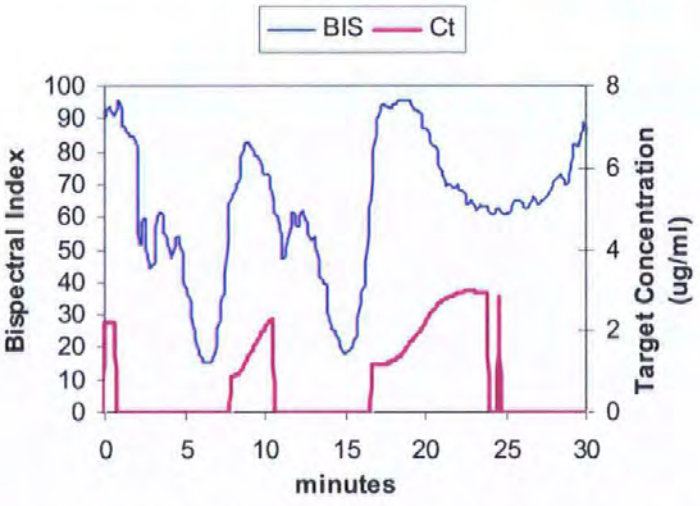
When the BIS value becomes greater than the target, the PID controller starts to increase the target effect site concentration used by the pharmacokinetic model to generate the infusion rate. However, the infused drug takes effect with delay or hysteresis, and before the drug effect can be measured, the BIS will continue rising, and the controller keeps increasing the target concentration. If the controller gains were too large for a particular subject, then excessive drug would have been given during this process, which consequently causes overshoot, i.e., BIS falls lower than the target. Theoretically, the longer the hysteresis is, the larger the overshoot would be. This is the reason why overshoot often happens after undershoot in response to stimulation, and could be one of the contributions to the BIS oscillation seen in subject 10 and 13.

The worst oscillatory BIS occurred in subject 13 on whom the CLAN system spent 22.6 minutes to stabilise the BIS near the end of the infusion. The BIS trends and predicted propofol concentrations in this subject are unique and interesting. The detailed result is given

in Figure 7-10.



(a) Bispectral Index (BIS) and resulted target concentration (Ct)



(b) target concentration (Ct), effect site concentration (Ce), and infusion rate (IR)

Figure 7-10 Bispectral Index (BIS), target concentration (Ct), effect site drug concentration (Ce), and infusion rate (IR) of the propofol infusion in volunteer 13

As discussed previously in relation to subject 10, the hysteresis and PID controller gains would have both contributed to the overshoots in subject 13. However another contribution to

the oscillation in the 13th subject would be the possible development of natural sleep that affects the Bispectral Index in the same way as the depth of anaesthesia (Sleigh et al., 1999). The additional BIS value the natural sleep adds on the top of the BIS value measured from the depth of anaesthesia could disappear immediately by stimulation. In a subject (volunteer) or a patient with epidural, there is no painful (nociceptive) input. Accordingly they may fall into natural sleep. If the resultant BIS is lower than the target, then the CLAN system will suspend infusion, which progressively withdraws the propofol from the patient. If there is external acoustic stimulation, the arousal may wake the patient in whom the drug concentration is insufficient to maintain unconsciousness in the absence of sleep.

The initial bolus caused overshoot in this subject (BIS=47), and the subject possibly developed natural sleep afterwards that could be the reason why the BIS value was further down to 15. There had been no drug infusion at all for 8.3 minutes after the initial bolus, and the BIS reached a minimum. During this period, the drug was progressively eliminated from the body, and the predicted effect site propofol concentration (Ce) dropped down to 1.1 mcg/ml when BIS was 16 and the subject opened his eyes. This is very similar to the recovery process of this subject in which the BIS value reached 91.2 when Ce=1.1 mcg/ml at the time 9.1 minutes after infusion had been terminated. The same predicted drug concentration (Ce) and the fact of eye-open suggest that the subject was likely awakened from natural sleep with a BIS value of 16. The drug infusion in response to the increasing BIS error prevented a larger extreme BIS value as seen in recovery period. Thereafter the natural sleep was possibly developed again during the second overshoot (low BIS). The infusion had been turned off for 6.0 minutes from 10.8 to 16.8 minutes after the start of infusion due to the second overshoot. Stimulation was given from the 15th minute, subsequently the subject was aroused earlier and the BIS reached a larger extreme value of 91.2 at the time of 17.2 minutes after the start of infusion.

People could fall asleep whilst anaesthetized. The Bispectral Index could then represent either the depth of anaesthesia, or the depth of natural sleep (Sleigh et al., 1999), or a mixture of both. After infusion has been stopped and the drug effect has reached its peak, with the possible existence of natural sleep the Bispectral Index could go up towards lighter anaesthesia at a smaller rate, or oscillate within a range, or even go further down. The BIS trend depends upon the depth of anaesthesia, the level of the possible natural sleep developed, and the external stimulation. Since a slow wave sleep could result in a BIS value as low as 20 with zero drug concentration (Sleigh et al., 1999), a low drug concentration with a significant low BIS value in a subject would suggest that the subject is in a deep sleeping state or an

altered state of "consciousness", and eventually the subject could be easily awakened by an external stimulation. The wakening drug concentration may vary in a wide range depending upon the pharmacokinetic and pharmacodynamic characteristics in individual patients, the depth of sleeping state and the level of external stimulation. When a subject wakes up from a low drug concentration, a sharp rise in BIS will be measured immediately.

Natural sleep has been modelled into a virtual patient with the following pharmacokinetic characteristics:

- t_peak = 0.5 minutes
- k10=0.03 min^{-1}
- k12=0.02 min^{-1}
- k13=0.01 min^{-1}
- k21=0.01 min^{-1}
- k31=0.008 min^{-1}

This patient is simulated with following methods and essential assumptions in calculating the drug concentrations with additional contribution from natural sleep to Bispectral Index:

- The BIS target is 65 (or equivalent initial effect site target concentration of 2.23 mcg/ml after conversion from the BIS target).
- The virtual patient develops natural sleep as soon as the calculated effect site drug concentration reaches 2.5 mcg/ml, and the virtual patient enters into the altered state of "consciousness" until the virtual patient wakes up.
- Bispectral Index is maintained below the target (deeper level of anaesthesia than the target) due to the contribution from natural sleep, and consequently no drug is infused any more.
- Drug concentrations in plasma and at effect site (Cp_2 and Ce_2 in Figure 7-11) steadily drop down due to the pause of drug infusion, which indicates that the anaesthetic level in the virtual patient becomes lower and lower whilst the Bispectral Index keeps below the target.
- An external stimulation happens as soon as the effect site concentration (Ce_2 in Figure 7-11) drops down to 1.5 mcg/ml, and the virtual patient is awakened by this stimulation.
- The Bispectral Index jumps to well above the target due to the sudden withdrawal of the contribution from natural sleep, and this results in a big bolus infusion that is designed in this simulation to bring the drug concentration in the virtual patient (Ce_2 in Figure 7-11) up to above 2.5 mcg/ml again.
- The above process repeats for 60 minutes.

The result of this computer simulation is shown in Figure 7-11 that is similar to the result obtained from the 13th volunteer (see Figure 7-10 (b)).

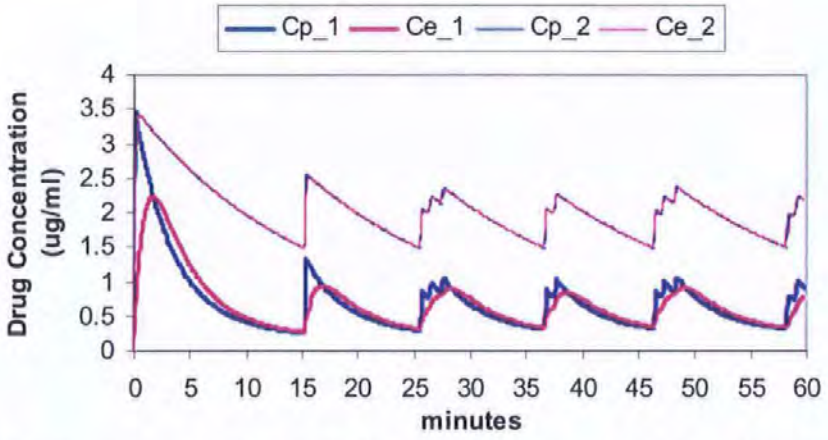


Figure 7-11 Computer simulation with natural sleep modeled in a virtual patient (upper thin lines: calculated drug concentrations (Cp_2, Ce_2) in the virtual patient, lower thick lines: drug concentrations (Cp_1, Ce_1) predicted by the reference model)

In the above simulation, the trend of predicted effect site concentration (Cp_1 and Ce_1 in Figure 7-11) shows the oscillatory property with repeatedly modelled natural sleep and external stimulation. However, it does not mean that the BIS oscillation will last forever in real clinical environment. In fact, the BIS in subject 10 and 13 were stabilised in 12.1 and 22.6 minutes, respectively. In subject 13, infusion was terminated at 25 minutes and then BIS started rising. The change of rate in BIS values became significantly low before the termination of infusion. This suggests that the BIS would have been kept stable for some time if the infusion continued.

The effect site concentration on which a patient would begin to develop natural sleep or be awakened by external stimulations might depend on a number of factors, such as the depth of anaesthesia, and the level of external stimulation. Therefore the values chosen in the simulation would not fit all patients but may demonstrate on what could happen with natural sleep and external stimulation.

The PK/PD parameters are chosen so that the initial bolus will induce a deep anaesthesia on which the development of sleep would be possible with BIS target of 65. If the desired depth of anaesthesia is deeper, say BIS value of 40 to 50 (or 4.14 to 3.36 mcg/ml after BIS to Ce conversion), then the same simulation result could be obtained from some of the virtual patients defined in Chapter 5.

Another important cause to the BIS oscillation measured in the subject 13 would be the inter-

subject pharmacodynamic variability. Clearly, this subject requires much less drug than any volunteers in this study to achieve the same BIS target.

Because no measurement on plasma drug concentration was made in any subject of this study, therefore there is no way to explore the pharmacokinetic variability in subjects for this study. However the pharmacodynamic variability in subjects during anaesthesia induction is shown in Figure 7-12.

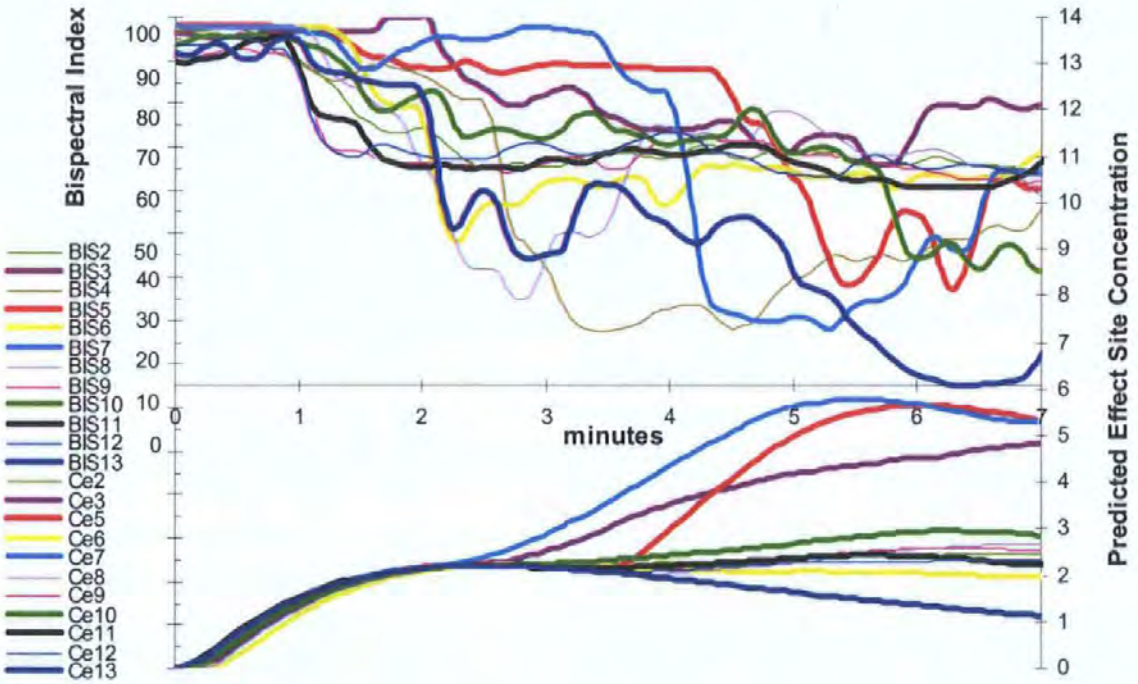


Figure 7-12 Bispectral Indexes (upper set of lines) and predicted effect site concentrations (in mcg/ml, lower set of lines) in induction

The initial bolus infusion achieved 2.23mcg/ml in predicted effect site concentration in all subjects in around 2 minutes. However the drug effect shown by the Bispectral Index differs in the subjects at the same time or shortly after. While the BIS target was achieved and stable in 4 subjects (subject 2, 9, 11, and 12), undershoot was developed in another 4 subjects (subject 3, 5, 7, and 10), and overshoot was developed in the others (subject 4, 6, 8, and 13). The BIS and predicted effect site concentration after the induction are shown in Figure 7-13. While the BIS was maintained stable at the same BIS target in most subjects, the predicted effect site concentration was maintained stable in different levels. The BIS and predicted

concentration in subject 3, 7, and 13 demonstrate the typical pharmacodynamic variability in this study.

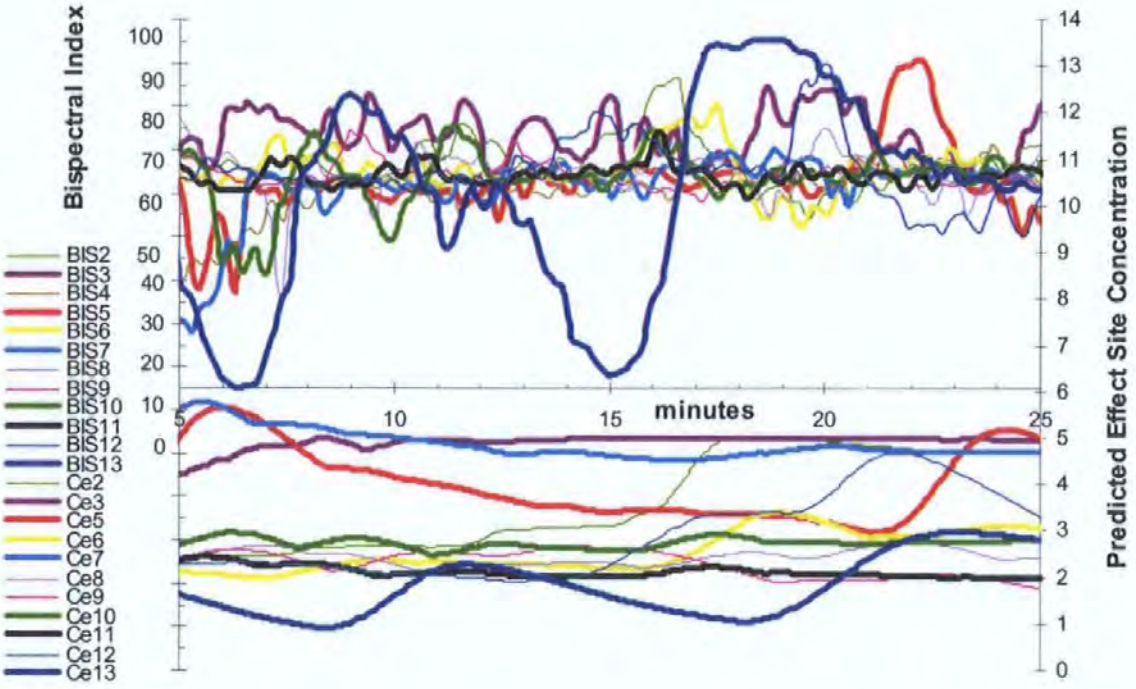


Figure 7-13 Bispectral Indexes (upper set of lines) and predicted effect site concentrations (in mcg/ml, lower set of lines) after induction

While subject 7 maintained a predicted concentration of 4.8(0.2) mcg/ml with a stable BIS of 63.7(3.0) at the target, the BIS in subject 3 was well above the target at 73.2(5.9) with a higher and stable predicted concentration of 5.1(0.1) mcg/ml. On the contrary, the BIS in subject 13 was oscillating between 93.1 and 15.4 before stabilised at the target, whereas the concentration was oscillating between 0.9 and 2.2mcg/ml and stabilised at 3mcg/ml.

Clearly, subject 13 needs much less drug then anyone else in this study to achieve the same BIS target. Because the amount of drug to be infused depends upon the BIS error and the PID controller gains, therefore, the gains used with subject 13 should have been significantly smaller. This would produce smaller changes in target effect site concentration for the reference model and hence less drug would be given. Otherwise, BIS oscillation is likely to occur.

This study demonstrates that there is no single non-adaptive PID controller and fixed reference PK/PD model that can encompass all patients in a population due to the inter-patient variability. To obtain optimal resultr fo all patients, an adaptive controller is ideal to provide more accurate infusion rates. Furthermore, any controller to be used to control depth of anaesthesia should be aware of and anticipate the clinical difference between anaesthesia and natural sleep, which the BIS cannot differentiate.

The CLAN system did not achieve the BIS target in the 3rd subject due to the maximal concentration limit of 5mcg/ml set for the first three subjects. The safety limit was then set for the individual subject just before the infusion started and made on-line modifiable for the successive experiments. If there were no such limit or the limit was set to a high enough value, the BIS target should have been achieved with a higher drug concentration. Though this result was not expected it shows the system's ability to ensure the safety of patients by setting a safety limit on predicted drug concentration.

7.5. Propofol/Nitrous Oxide Sedation on Volunteers

7.5.1. Objective

Nitrous Oxide (N_2O) is commonly used as a supplement to propofol infusions to provide analgesia and additional hypnosis. After the success in propofol sedation study on volunteers, we further tested the CLAN system for propofol/N_2O sedation on another set of fit volunteers. The objective of this study is to investigate whether there is any interaction between the two drugs (propofol and nitrous oxide) as far as measured BIS is concerned.

7.5.2. Methods

For all subjects selected for this study, no premedication was given before the experiments. The BIS target was again set to 65 to achieve hypnotic effect (Baker, Sleigh and Smith, 2000) in the subjects. Figure 7-14 shows the experiment protocol for this study.

The CLAN system started from 5 minutes baseline recording without infusion. In the meantime, the volunteers were told to keep quiet with eyes closed. After the base-line recording, a 20-minute propofol infusion was given to all volunteers for the induction and maintenance of sedation, and then 15-minute propofol infusion *with* the uptake of 50% N_2O followed by another 15-minute propofol infusion *without* nitrous oxide uptake. The infusion was terminated at the 50th minute while the CLAN system continued to record clinical data for 10 minutes or longer for the recovery of the subjects. All other methods described in

Section 7.3 apply.

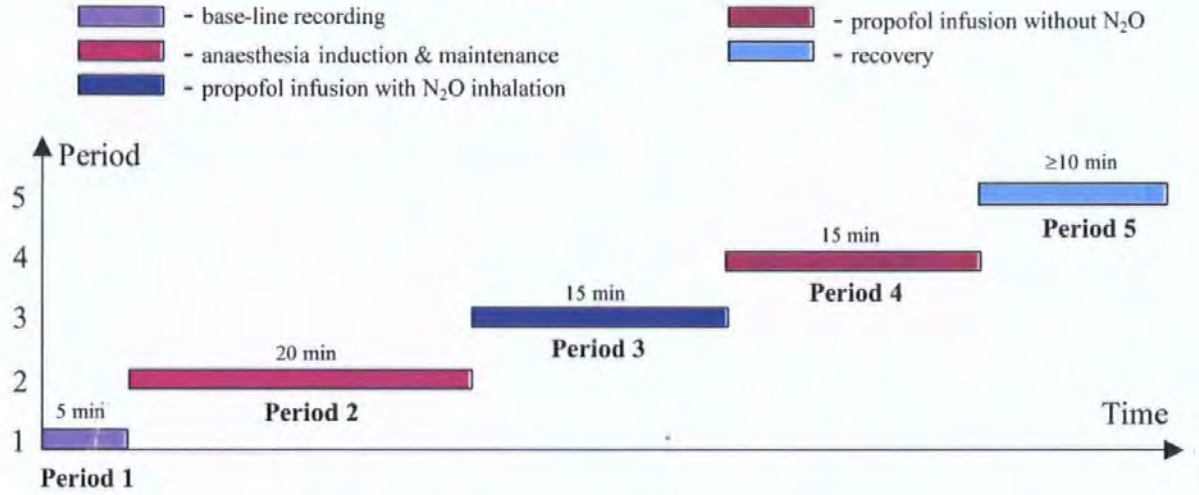


Figure 7-14 Experiment protocol for volunteer study with propofol and N_2O

Because overshoot happened too often following undershoot in previous study, therefore the PID controller gains were adjusted through computer simulation to achieve following goals:

- Reduce the drug administration when a big BIS error occurs in case the hysteresis is long (e.g., during induction or subject is awaked by stimulation). This was done by choosing a smaller integration gain Ki.
- Increase the response speed by using a bigger differential gain Kd. This means the bigger positive difference between the two continuous BIS samples, the more drug will be given, and the infusion will be shut off earlier when the BIS drops due to this change.
- Increse the proportional gain Kp accordingly to improve the response speed.

A new set of PID controller gains meeting above requirements were manually tuned from computer simulation and used in this study:

Kp=0.0024
Ki=0.00001
Kd=0.18

7.5.3. Results

Eight fit volunteers (ASA I&II, 23-41 year, 62-97 kg, 5 men and 3 women) entered into this

study, the characteristics of these subjects are summarised in Table 7-5. Sedation was achieved in all subjects with or without the presence of nitrous oxide.

For best presenting the results from this study, the measured Bispectral Index (BIS_i for the i^{th} volunteer) and predicted propofol concentration in plasma (Cp_i for the i^{th} volunteer) and at effect site (Ce_i for the i^{th} volunteer) in the eight subjects are split into two parts as shown in Figure 7-15, Figure 7-16, and Figure 7-17.

Table 7-5 Characteristics of the volunteers for propofol/N_2O sedation

Volunteer	1	2	3	4	5	6	7	8	Mean (SD)
Gender	M	M	F	F	M	M	F	M	N/A
Age (years)	30	38	41	31	23	29	30	41	32.9 (6.4)
Weight (kg)	80	86	76	73	73	97	62	63	76.3 (11.6)
Height (cm)	175	185	168	160	173	192	170	166	173.6 (10.4)

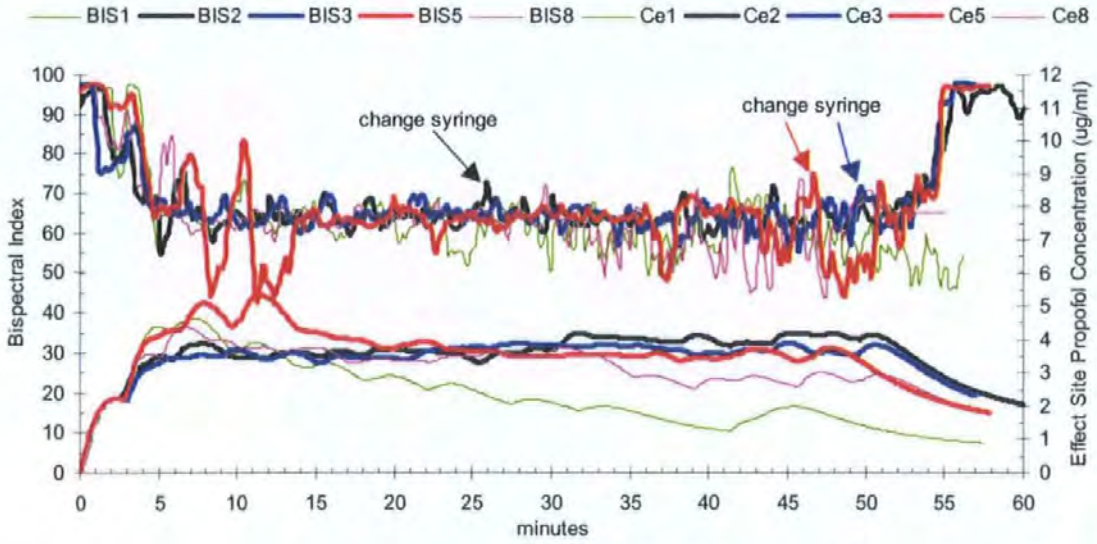


Figure 7-15 Expected BIS trends and predicted effect site propofol concentrations in 5 volunteers in propofol/N_2O study (upper: BIS, lower: predicted concentration)

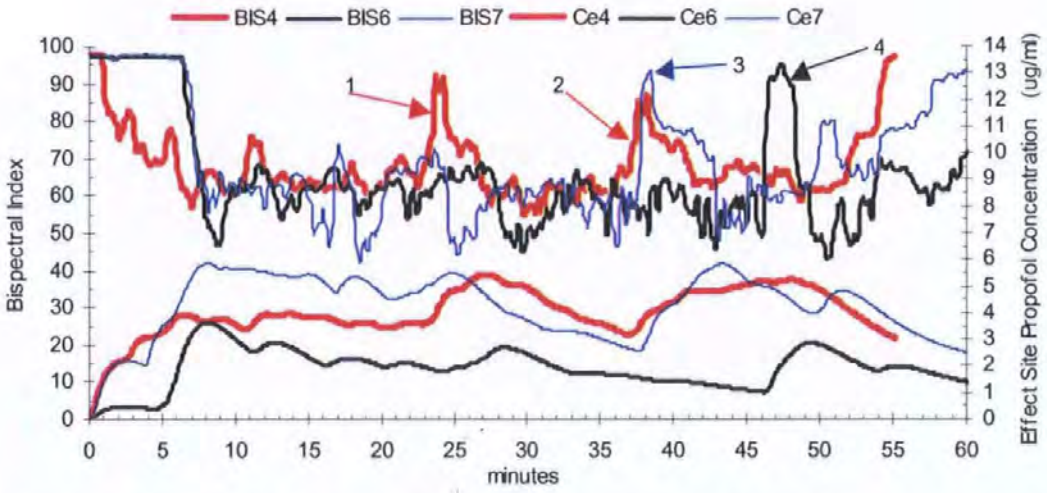


Figure 7-16 Expected BIS trends and predicted effect site propofol concentrations in 3 volunteers in propofol/N_2O study (upper: BIS, lower: propofol concentration, arrows 1~4: subjects were aroused by environmental noises)

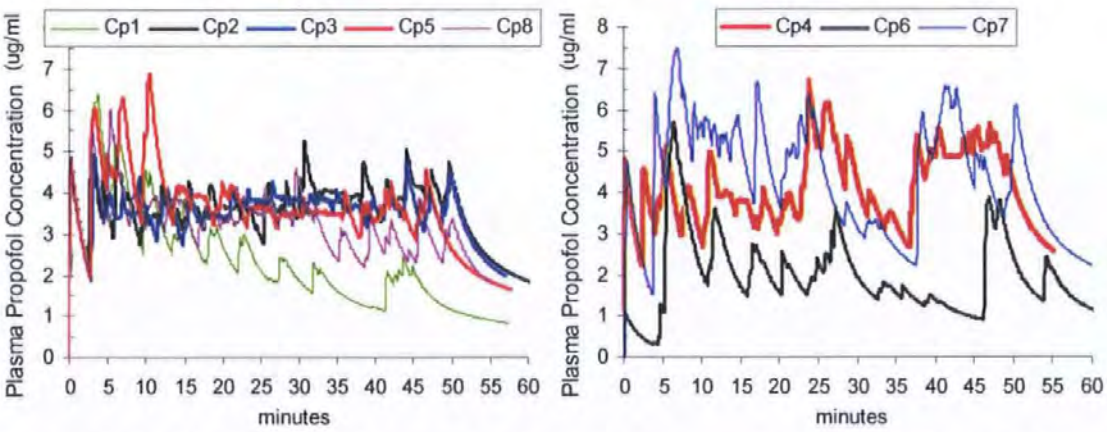


Figure 7-17 Plasma propofol concentrations in 8 volunteers in propofol/N_2O study

Figure 7-15 shows the Bispectral Indexes (BIS) and predicted effect site propofol concentrations (Ce) in five volunteers (subject 1, 2, 3, 5, and 8) while Figure 7-16 presents those in the other three volunteers (subject 4, 6, and 7). The predicted plasma propofol concentrations (Cp) in the eight subjects are given in Figure 7-17. In all three figures, the x axis shows the time in minutes after the start of infusion.

Table 7-6 Induction time, BIS stable time, recovery time, and the predicted wake concentration (Ce) in the 8 volunteers in propofol/N_2O sedation study

	Volunteer								Mean
	1	2	3	4	5	6	7	8	(SD)
Induction Time (min)	4.7	5.0	4.5	6.2	4.7	7.7	7.4	4.6	5.6 (1.3)
BIS Stable Time (min)	4.7	6.8	4.5	12.2	13.7	7.7	7.4	6.5	7.9 (3.3)
Recovery Time (min)	N/A	5.5	4.9	4.4	4.9	8.0	7.8	N/A	5.9 (1.6)
Wake Ce (mcg/ml)	N/A	2.76	2.76	3.28	2.15	1.12	2.91	N/A	2.5 (0.8)

Anaesthesia induction was successful in all subjects. The CLAN system achieved the BIS target in 5.6(1.3) minutes (induction time as defined in Section 7.3), and stabilised the BIS at 62.9(5.4) in 7.9(3.3) minutes (BIS stable time as defined in Section 7.3). After 20 minutes of infusion, the subjects breathed 50% N_2O for 15 minutes. The addition of N_2O did not change the BIS trends in subjects. When the two drugs were administered simultaneously, the BIS was maintained at 62.7(5.4). Thereafter, the propofol infusion continued for another 15 minutes without N_2O breathed. However, the withdrawal of N_2O is associated with the drop and oscillation of BIS in some subjects, and the BIS measured during this period was 62.6(8.4). Following the end of propofol infusion, the BIS value in the 8 subjects reached 90 or over in 5.9(1.6) minutes (recovery time as defined in Section 7.3). The overall Mean(SD) value of BIS in all subjects is 62.7(6.5), which is calculated from the BIS values in all subjects after the induction up to the end of propofol infusion.

The individual anaesthesia induction time, the individual BIS stable time, the individual recovery time, and the predicted wakening concentration, as defined in Section 7.3, are listed in Table 7-6. While Table 7-7 and Table 7-8 show the Mean(SD) values of BIS and predicted effect site concentration Ce in individual volunteers at different periods.

Table 7-7 The Mean(SD) values of BIS in volunteers in propofol/ N_2O sedation study

Volunteer / Period	1	2	3	4	5	6	7	8	All
Period 2	63.7	64.1	64.6	64.0	62.1	60.7	59.5	64.4	62.9
	(3.0)	(3.3)	(2.3)	(3.5)	(9.3)	(4.5)	(6.8)	(4.5)	(5.4)
Period 3	60.6	64.4	64.9	65.7	63.8	58.5	60.5	62.7	62.7
	(4.4)	(2.2)	(1.9)	(8.2)	(2.0)	(6.1)	(6.3)	(3.6)	(5.4)
Period 4	60.3	63.9	63.4	67.7	60.9	60.8	65.7	58.2	62.6
	(5.2)	(2.2)	(3.3)	(6.2)	(7.3)	(13.6)	(11.4)	(6.9)	(8.4)
All Periods	61.6	64.1	64.3	65.8	62.3	60.0	61.9	61.8	62.7
	(4.6)	(2.7)	(2.7)	(6.5)	(7.0)	(8.9)	(8.9)	(5.8)	(6.5)

*Period 2/3/4 – maintenance period before/during/after the inhalation of N_2O, see Figure 7-14

Table 7-8 The Mean(SD) values of predicted effect site propofol concentration in individual volunteers in propofol/ N2O sedation study

Volunteer / Period	1	2	3	4	5	6	7	8	All
Period 2	3.6	3.6	3.5	3.7	4.4	2.3	5.4	3.7	3.7
	(0.59)	(0.13)	(0.10)	(0.16)	(0.47)	(0.93)	(0.28)	(0.29)	(0.95)
Period 3	2.3	3.6	3.8	4.4	3.6	2.1	4.3	3.5	3.4
	(0.31)	(0.23)	(0.12)	(0.68)	(0.14)	(0.29)	(0.78)	(0.15)	(0.88)
Period 4	1.6	4.0	3.7	4.6	3.5	1.6	4.4	2.8	3.3
	(0.22)	(0.10)	(0.10)	(0.64)	(0.12)	(0.52)	(1.08)	(0.12)	(1.19)
All Periods	2.5	3.8	3.6	4.3	3.9	2.0	4.7	3.4	3.5
	(0.94)	(0.25)	(0.16)	(0.66)	(0.51)	(0.71)	(0.94)	(0.44)	(1.03)

7.5.4. Discussion

In this study, the CLAN system was tested on 8 volunteers for propofol sedation with and without inhalation of N_2O. A new set of PID controller gains was used in this study. In computer simulation, this set of gains gives roughly the same results on the nine typical pseudo patients as presented in Chapter 5. In clinical experiments with the new controller gains, the CLAN system is expected to achieve a smoother anaesthesia induction due to the smaller Ki, more quickly to re-achieve the BIS target when a subject becomes inadequately

anaesthetized with less possibility of overshoot because of a bigger Kp and Kd and a smaller Ki. However, the induction time is expected to be longer if undershoot is developed. This is because less drug will be given by using a smaller integration gain Ki and the increase of proportional gain Kp and differential gain Kd has no effect on increasing the infusion rate when BIS drops. These are actually what happened in the clinical experiments.

The BIS trends for the 8 subjects shown in Figure 7-15 and Figure 7-16 look better than the BIS trends presented in previous study. This is confirmed by the statistical analysis on the BIS data shown in Table 7-7.

As shown in Table 7-9, the BIS maintained in the 8 subjects in this study is slightly lower than that in previous study. This is mainly because of the use of the new set of controller gains, which improved the response speed and resulted in fewer occurrences of inadequate anaesthesia. The second reason is that no stimulation was given during the entire course of infusion except for the audio alarm from the infusion pump when the syringe was nearly empty or completely empty.

Table 7-9 Comparison of mean(SD) values of BIS maintained in different periods in this and previous studies

Mean(SD) BIS	**Period 2**	**Period 3**	**Period 4**	**All Periods**
This Study	62.9(5.4)	62.7(5.4)	62.6(8.4)	62.7(6.5)
Prev. Study	63.1(8.2)	66.1(11.4)	63.8(5.3)	63.9(8.7)

*all values listed in the table are in Mean(SD).

The use of new controller gains also provided a much smoother induction performance. The maximal overshoot developed was a BIS value of 46.9 in subject 6 during anaesthesia induction because less drug was given than in the previous study when BIS target was not yet achieved with big positive BIS errors. However, as expected this performance was at the cost of a longer time for the CLAN system to achieve the BIS target (5.6(1.3) vs 3.2(1.4) minutes), but the time spent by the CLAN system to stabilise the BIS did not differ in the two studies (7.9(3.3) vs 7.2(6.0)) and was more consistent in this study (i.e., much smaller deviation (SD): 3.3 vs 6.0) (please refer to Table 7-10).

Table 7-10 Induction time, BIS stable time, and recovery time in two studies

	Induction Time	**BIS Stable Time**	**Recovery Time**
This Study	5.6(1.3)	7.9(3.3)	5.9(1.6)
Prev. Study	3.2(1.4)	7.2(6.0)	6.4(2.4)

*all values listed in the table are in Mean(SD).

Although the overall control performance has been significantly improved over the previous study, BIS oscillation, seen in subject 10 in the previous study, occurred in subject 5 (between 6.4 and 13.8 minutes after the infusion started) and subject 7 (15 to 28.4 minutes) of this study. Inappropriate controller gains and hysteresis could be again the cause of these oscillations. This study demonstrates again that there is no single set of controller gains that works on all subjects.

Due to the long infusion time in this study, one syringe of propofol was not enough for some subjects. However, the change or refilling of syringes delayed the infusion up to 2 minutes, and the infusion pump issues an audio alarm when the syringe is nearly empty, which imposed some stimulation upon the subjects. This was associated with the rise of BIS to various degrees in some volunteers (volunteer 2-5, indicated by the marks with "change syringe" in Figure 7-15 and arrows in Figure 7-16).

As with subject 13 in previous study, natural sleep could possibly be developed in subjects 4, 6, and 7 in this study. To investigate why the large undershoots (marked by arrows 1, 2, 3, and 4 in Figure 7-16) were developed in subjects, Table 7-11 lists the no infusion times during which the predicted concentration dropped before these undershoots occurred, and the predicted effect site concentrations at the time these subjects were aroused. The individual times at which they were aroused, recovery times and wakening concentrations of the three subjects are also listed in the table for comparison purposes.

Table 7-11 Characteristics of the large undershoots developed in subjects 4, 6, and 7

	Recovery time (min)	Wakening concentration*	Ce when subjects were aroused*	Time aroused (min)	No infusion period
Subject 4	4.4	3.28	3.56	23	0.8
Subject 4	4.4	3.28	3.17	37	9.6
Subject 6	8.0	1.04	1.02	46.6	17.6
Subject 7	7.8	2.91	2.53	38	12.6

* unit is mcg/ml

In subjects 4, 6, and 7, as marked by arrows 1~4 in Figure 7-16, four large undershoots were developed. Before the first undershoot (at t=23 minute, Figure 7-16) developed in subject 4, the predicted propofol concentration was stably maintained at 3.56 mcg/ml that is slightly over the eventual awakening concentration 3.28 mcg/ml. This suggests that the anaesthetic level in this subject may have been so low that he could be easily aroused by external stimulation such as noises. However before all the other undershoots, due to the long absence of infusion (see Ce trends in Figure 7-16 and Table 7-11) the predicted concentrations dropped below individual wakening concentrations recorded in recovery. With these drug concentrations in the subjects, external stimulation could easily arouse them. The undershoot which happened at t=37 minute in subject 4 for example, was initiated by the audio stimulation from the pump alarm reminding of change of syringe.

Before the undershoots (marked by arrows 2~4 in Figure 7-16) developed in subjects 4, 6, and 7, the BIS had been maintained under the BIS target for 9.6 minutes, 17.6 minutes, and 12.6 minutes, respectively in the three subjects without drug infusion. These no-infusion times are significantly shorter than their recovery times (see Table 7-11), which strongly suggest that the subjects had developed natural sleep before they got aroused.

The addition of N_2O did not significantly change the BIS pattern, and it did not break the maintenance of the BIS target. However, its withdrawal was associated with moderate oscillation of BIS in subject 1, 3, 5, and 8 (see Figure 7-15). These are consistent with published findings (Rampil et al., 1998; Barr et al., 1999; Hirota et al., 1999) in which all authors claimed that the addition of N_2O did not significantly change BIS values during propofol sedation. However, Rampil and colleagues (1998) revealed that "N_2O (50%) increased theta, beta, 40-50 Hz, and 70-110 Hz band powers" and "the abrupt decreases from higher to lower (N_2O) concentrations frequently evoked a profound, transient slowing of

(EEG) activity". The change of EEG activity in lower and higher bands of frequencies observed by these investigators may well cause changes in BIS values once the inhalation of N_2O was suddenly stopped.

Significant inter-variability in subjects was shown by the BIS values during induction of anaesthesia in this study. In fact, all subjects except for subject 6 developed various degrees of undershoot in response to the same dose (μg/kg) of initial bolus. Different amounts of extra drug were subsequently given by the CLAN system to achieve the same BIS target. Furthermore, different levels of predicted concentrations throughout the infusion process also suggest the existence of inter-subject pharmacodynamic variability. The maximal and minimal predicted stable concentration maintained were 5.4~5.8mcg/ml in subject 7 and 2~2.9mcg/ml in subject 6.

The only problem encountered in this study was the induction of anaesthesia in subject 6. Because the syringe was not well seated on the pump, the CLAN system twice failed to give the full initial bolus infusion. The CLAN system however eventually gave the full initial bolus at the third start in 5 minutes, and successfully achieved the BIS target. This caused an overshoot to 48.2 in BIS possibly due to the previous two partial infusions. The infusion protocol was therefore extended for another 5 minutes to allow stabilisation. The calculation of predicted propofol concentrations in plasma and at effect site was not affected by the syringe failure (see Figure 7-17).

7.6. Propofol Sedation in Patients Undergoing Knee Surgery

7.6.1. Objective

After the evaluation of the CLAN system on fit volunteers (n=21), the CLAN system was subsequently further tested on patients undergoing reconstructive knee surgery under epidural anaesthesia. The objective of this test was to examine the control performance of the CLAN system on depth of anaesthesia in a surgical environment. Studying patients with an epidural in-situ meant that the patients were not dependent on the CLAN system for surgical anaesthesia.

7.6.2. Methods

A lumber epidural catheter was placed under local anaesthesia either before (n=4) or after (n=2) starting sedation, and a regional block established. The BIS target was initially set at 65(Baker, 2000) and then adjusted at clinical discretion. Closed loop sedation was functioning

before the start of surgery and was maintained throughout. The general methods described in Section 7.2 applied.

7.6.3. Results

Six male patients (ASA status I-II, age 25-39 years, weight 70-100 kg) have been studied with another patient entered into the study without sedation because of a broken cable. Clinically satisfactory results were obtained from three patients, however the results from the other three were not clinically acceptable due to oscillation in BIS. Table 7-12 gives the individual characteristics of these patients.

Table 7-12 Characteristics of the six patients undergoing knee surgery

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**Mean(SD)**
Gender	M	M	M	M	M	M	
Age (years)	27	25	35	29	31	39	31 (5.2)
Weight (kg)	85	80	83	100	70	99	86.2 (11.5)
Height (cm)	190	185	178	188	173	178	182 (6.7)

Sedation at the initial BIS target was established in 7.8(1.9) minutes, and subsequently the BIS target was manually adjusted when necessary to meet clinical requirements for the patient undergoing surgery. The BIS error between the measured BIS and BIS targets in the six patients after the induction was –3.6(10.9), whilst the predicted effect site propofol concentration was maintained at 4.0(2.1) mcg/ml during the same infusion period. The recovery time for the patients was 10.2(1.2) minutes.

In the first 4 patients, the changes of patient position and other stimuli before the surgery started (e.g., the placement of the lumber epidural catheter, transfer of patient from anaesthesia room to surgery room, etc.) were associated with rapid changes of BIS and various levels of consciousness. In two patients (patient 2 and 3), during the surgery, when stimulation was confined to the leg (i.e. blocked by the epidural), a condition resembling natural sleep was possibly developed, and they awakened from a BIS value of 46 or 47 with predicted effect site concentration (Ce) of 1.08 mcg/ml or 0.95 mcg/ml, respectively.

Table 7-13 lists the induction/recovery times and the predicted wakening concentration in individual patients. While Table 7-14 lists the measured BIS errors and predicted concentrations in the six patients. Figure 7-18 shows the BIS, BIS target, and predicted propofol concentrations in plasma and at the effect site in a single patient (patient 2).

Table 7-13 Induction time, recovery time, and the predicted effect site propofol wakening concentration (Ce) of the six patients undergoing knee surgery

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**Mean(SD)**
Induction (min)	9.3	8.3	4.7	8.8	9.4	6.3	7.8(1.9)
Recovery (min)	10.9	9.0	N/A*	11.5	N/A*	9.3	10.2(1.2)
Wakening Ce (mcg/ml)	1.34	1.23	N/A*	2.82	N/A*	2.25	1.91(0.76)

* because the operating theatre had to be made available for the next patient, and the data recordings on patient 3 and 5 were terminated before the patients awakened.

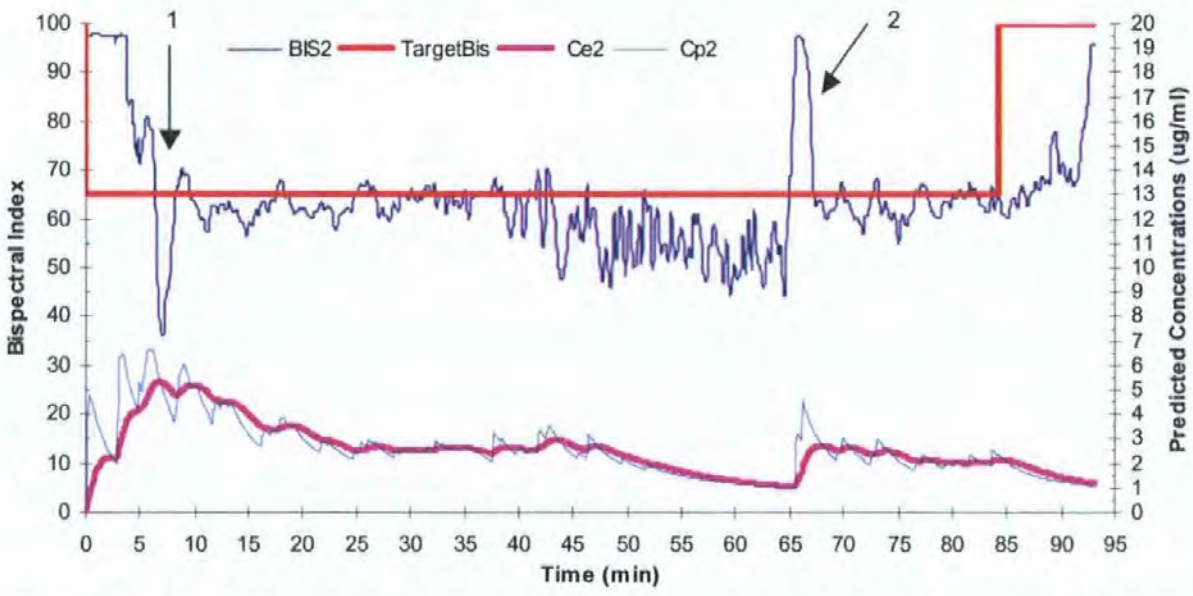


Figure 7-18 BIS (upper thin line) and its target (upper thick line) and predicted plasma (lower thin line) and effect site (lower thick line) propofol concentration in a patient (arrow 1- over-shoot in anaesthesia induction; arrow 2 – patient unexpectedly awakened from natural sleep)

Table 7-14 The means (standard deviations) of BIS errors and predicted effect site propofol concentrations (Ce) in the six patients undergoing knee surgery

Patient	1	2	3	4	5	6	All
BIS Error	-4.4(15.8)	-3.6(7.3)	-7.0(12.2)	-1.3(7.3)	-4.5(7.1)	-2.8(10.9)	-3.6(10.9)
Ce (mcg/ml)	2.4(1.1)	2.6(0.9)	2.7(1.1)	6.4(1.4)	2.8(1.0)	4.5(1.2)	4.0(2.1)

As shown in Figure 7-18, two extra boluses were given to this patient after the initial bolus by the CLAN system to achieve the sedation target, stable sedation was established after the over-sedation (indicated by the arrow marked with '1'). Between the 45th and 65th minute BIS remained below the target for 20 minutes without drug infusion at all due to the apparently developed natural sleep, consequently the patient 'awoke'. This resulted in the sharp rise in BIS (indicated by the arrow marked with '2') a few seconds later. However, the BIS target was achieved again quickly and maintained until the termination of the sedation.

7.6.4. Discussion

In this study, the CLAN system controlled the propofol infusion on real patients in an environment different from that in previous studies. In the patients with epidurals in place, all painful (nociceptive) input is cut off by the regional anaesthesia, therefore the CLAN system is only trying to produce sedation in the patients. In theory, the only difference in drug infusion between this situation and that in previous studies without nitrous oxide breathed is that the patients were in an operating theatre where not all the other inputs were controllable, particularly noise and vibration. A patient having an orthopaedic operation may feel no pain, but their ears will hear noise and their sensory system will also detect vibration in parts of the body that are not blocked by the epidural. Both of these may cause the patient to demonstrate arousal.

Due to the presence of various stimulations from the operating theatre, the drug delivery control performance in this study was worse than that achieved in the fit volunteers in previous studies. This can be seen from the standard deviations of BIS errors measured and of the predicted effect site propofol concentrations maintained in all patients listed in Table 7-14. BIS oscillation still happened in some patients, for example, patient 4 as shown in Figure 7-19. Inter-patient variability, hysteresis and controller gains remained to be the main causes

of the unsatisfactory control performance in these situations.

Natural sleep, which would cause a large BIS jump when broken by stimulation, possibly developed in all patients except for patient 6. At low BIS values, two patients (patient 2 and 3) opened their eyes due to the break of possible natural sleep, while others demonstrated various levels of arousal such as arm or body movement.

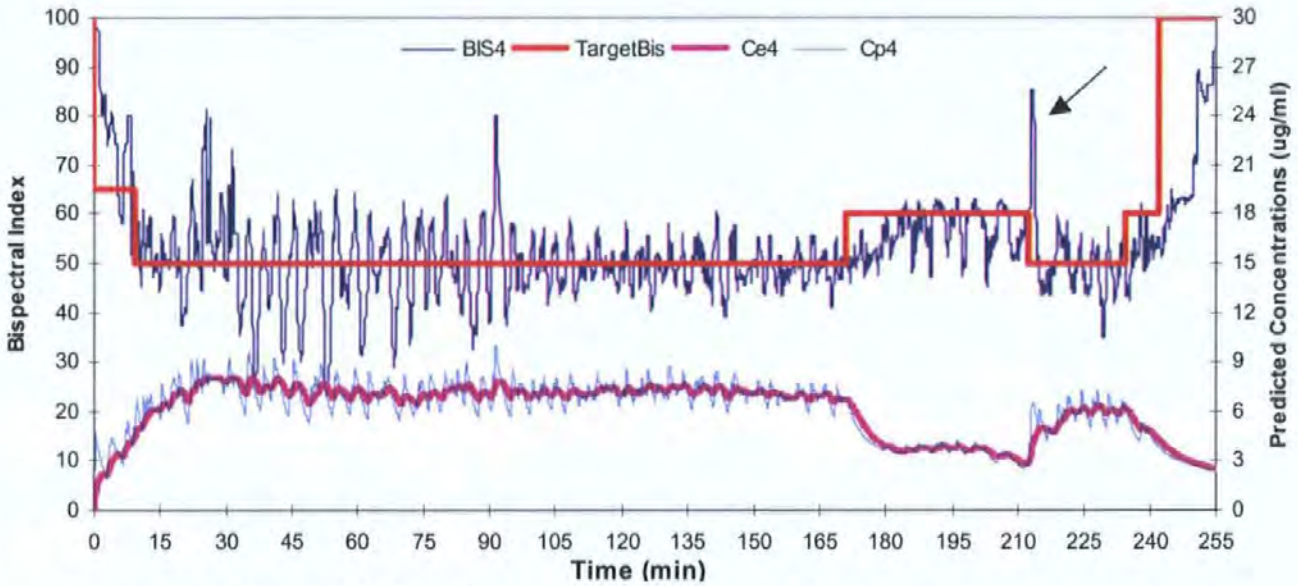


Figure 7-19 Bispectral Index (BIS4) and predicted propofol concentrations (Ce, Cp) in patient 4 undergoing knee surgery (the patient unexpectedly awoke followed by the BIS jump indicated by the arrow)

Table 7-15 lists all occurrences of possible natural sleep developed in the patients with the predicted effect site concentrations at which the patients were aroused thereafter. It also lists the wakening concentration and the recovery time as defined in Section 7.3, and the time period over which there was no infusion at all until the patient was awakened. With patients 3 and 5, the BIS recordings were terminated at the end of surgery before recovery due to the tight schedule of the operating theatre. Patient 3 opened his eyes at the predicted concentration listed in the table, whilst body movement was observed in patient 5 at the listed concentration (predicted).

Generally, if natural sleep had been developed when the measured BIS was below the BIS target, there would be no drug infusion if the contribution from the natural sleep to the depth of anaesthesia could keep the BIS below the target. However, when the drug concentration dropped close to or below the concentration at which the patient should have been awakened if there were no natural sleep developed, then at this time, the natural sleep developed would easily been broken by an external stimulation. In another words, this process is no different from the recovery process at the end of an experiment.

Table 7-15 Identified natural sleep developed in patients undergoing knee surgery

	Recovery time (min)	**Wakening concentration***	**Ce when subjects were aroused***	**No infusion period (min)**
Subject 1	10.9	1.34	1.16	11.6
Subject 1	10.9	1.34	0.76	20.8
Subject 2	9.0	1.23	1.08	12.9
Subject 3	N/A**	N/A**	0.95	29.2
Subject 4	11.5	2.82	2.91	5.2
Subject 5	N/A**	N/A**	1.34	14.3

*unit in mcg/ml

** because the operating theatre had to be made available for the next patient, and the data recordings on patient 3 and 5 were terminated before the patients awakened..

7.7. Total Intravenous Anaesthesia on Patients Undergoing Back Surgery

7.7.1. Objective

Total intravenous anaesthesia or general anaesthesia, during which an intravenous hypnotic and an intravenous analgesic are infused simultaneously, is popular for surgery due to their

property of rapid onset and quick recovery. All previous studies were designed to test the closed-loop control of propofol infusion under various clinical environments, and in this study the CLAN system was further tested for delivery of total intravenous anaesthesia on patients undergoing back surgery.

7.7.2. Methods

Propofol infusion was controlled by the closed-loop system by on-line monitoring of the Bispectral Index as in previous studies, whilst alfentanil infusion was controlled by an open-loop TCI system. The two drugs were delivered simultaneously.

To achieve adequate level of anaesthesia in patients for the surgeries under general anaesthesia, the BIS target was initially set to 50, while various initial effect site alfentanil concentration targets (100 ng/ml to 200 ng/ml) were set for individual patients. The choice of alfentanil targets and BIS target were based upon clinical research by Vuyk and colleagues (1995b) who found out through clinical study and computer simulation that the optimal propofol and alfentanil concentrations are 3.5 mcg/ml and 85 ng/ml, respectively (for female gynaecology patients). These target settings were found by Vuyk et al. (1995b) to be satisfactory both with respect to intra-operative anaesthetic conditions and speed of recovery. This is supported by another clinical report from the same investigator. The propofol target concentration of 3.5 mcg/ml corresponds to the converted BIS target of 49 by use of the population average pharmacodynamic model presented earlier. The BIS target of 50 in general anaesthesia is also supported by some other clinical studies (Morley et al., 2000; Struys et al., 2001).

Both the BIS target and the target alfentanil concentrations were adjusted at the clinical judgement of the anaesthetist during surgery to meet the dynamic clinical requirements. Closed loop controlled hypnosis and open loop controlled analgesia were maintained throughout surgery.

The minimum effect site propofol concentration was set at 2 mcg/ml to all patients and could be manually adjusted on-line at clinical discretion. This would reduce the possibility of sudden and large BIS rises if natural sleep developed.

The BIS overshoot threshold value (-2.5) and BIS prediction, as described in Section 6.6.5, were used in this study for the CLAN system to resume the infusion earlier when overshoot occurred. This mechanism would help prevent large undershoot immediately following an overshoot.

The BIS algorithm in the Aspect EEG Monitor A1000 was updated from version 3.12 to version 3.30. The only change in monitor settings is Bispectral Smoothing, which was changed from "off" to "15 seconds", because the "off" option is no longer available and "15 seconds" is the shortest setting for Bispectral Smoothing. This introduces BIS delay of 15 seconds. Except for this difference, the other methods described in Section 7.2 apply to this study.

7.7.3. Results

Nine patients (age 30-68 years, weight 56-98 kg, 7 men and 2 women) entered this study. The experiment failed on two of them (patient 5 and 6) due to broken EEG electrode leads, and the CLAN system delivered both propofol and alfentanil using open-loop TCI control in these two patients. These two patients are therefore excluded from the data analysis. The broken EEG electrode leads also affected the BIS values in another two patients during recovery. Clinically satisfactory results were obtained during this study. The patient characteristics are listed in Table 7-16.

Table 7-16 Characteristics of patients in the study of total intravenous anaesthesia

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Mean(SD)**
Gender	M	F	M	F	M	M	M	M	M	
Age (years)	33	41	31	50	49	54	30	53	68	45.4(12.7)
Weight (kg)	91	93	70	56	89	98	54	82	67	77.8 (16.5)
Height (cm)	180	157	168	165	183	189	155	173	157	169.7 (12.4)

The CLAN system quickly induced anaesthesia in patients in 3.04(1.77) minutes, and anaesthesia was successfully maintained with a BIS error of –3.5(6.6) between the measured BIS and BIS targets in all patients after the induction until the propofol infusion was stopped. The negative BIS error indicates that the level of hypnosis maintained is deeper than the targets. After the anaesthesia induction, the predicted effect site concentration (Ce) was maintained at 4.29(1.28) mcg/ml. The patients became responsive or woke up within 12.02(2.52) minutes (recovery time) after the termination of infusion, and at which time the predicted effect site propofol concentration, or the predicted wakening concentration as defined previously, was 1.97(0.6) mcg/ml. The induction time, recovery time, and the

wakening concentration are listed in Table 7-17. While the BIS error and predicted effect site propofol concentration maintained in individual patients are shown in Table 7-18.

Table 7-17 Induction time, recovery time, and the predicted wake concentration (Ce) in the 9 patients under general anaesthesia

Patient	1	2	3	4	5	6	7	8	9	Mean(SD)
Induction Time (min)	1.9	1.58	2	5.4	N/A	N/A	5.75	2.75	1.9	3.04(1.77)
Recovery Time (min)	12.75	13	9.75	9.48	N/A	N/A	10.91	N/A*	16.2	12.02(2.52)
Wakening Ce (mcg/ml)	1.79	2.44	2.23	1.35	N/A	N/A	2.74	N/A*	1.27	1.97(0.6)

*data recording stopped before the patients became responsive or woke up

Table 7-18 BIS errors and predicted effect site propofol concentrations in the 9 patients under general anaesthesia

Patient	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*All*
BIS Error	-1.1(4.6)	-2.4(8.5)	-3.2(7.0)	-4.8(3.4)	N/A	N/A	-3.9(5.9)	-2.4(6.7)	-4.7(8.3)	-3.5(6.6)
Ce (mcg/ml)	4.4(0.7)	4.8(1.1)	4.9(0.9)	2.9(0.6)	N/A	N/A	5.1(0.8)	4.9(0.8)	3.0(1.1)	4.3(1.3)

The same initial bolus (mg/kg), which was calculated from the initial BIS target of 50, was given to all patients, and this caused undershoot in 3 patients (such as patient 4 shown in Figure 7-20) and overshoot in 2 patients (BIS dropped down to 31.8 or 35.1). However, the CLAN system managed to achieve the BIS target and stabilised the BIS. Alfentanil infusion was started at the same time as the propofol infusion with various initial targets (see Figure 7-21). Both BIS target and alfentanil target concentration were changed at clinical discretion. In comparison with previous patient study, the induction in this study with presence of alfentanil was significantly quicker, and BIS trends were much smoother with less occurrence of BIS oscillation throughout surgery. In spite of the synergistic interaction (Vuyk et al., 1995b) between propofol and alfentanil, the presence or increase/decrease of alfentanil concentration did not change the Bispectral Index. Figure 7-20 and Figure 7-21 show the

measured BIS trend, predicted propofol and alfentanil concentrations in plasma (Cp) and at effect site (Ce) in a single patient (patient 4).

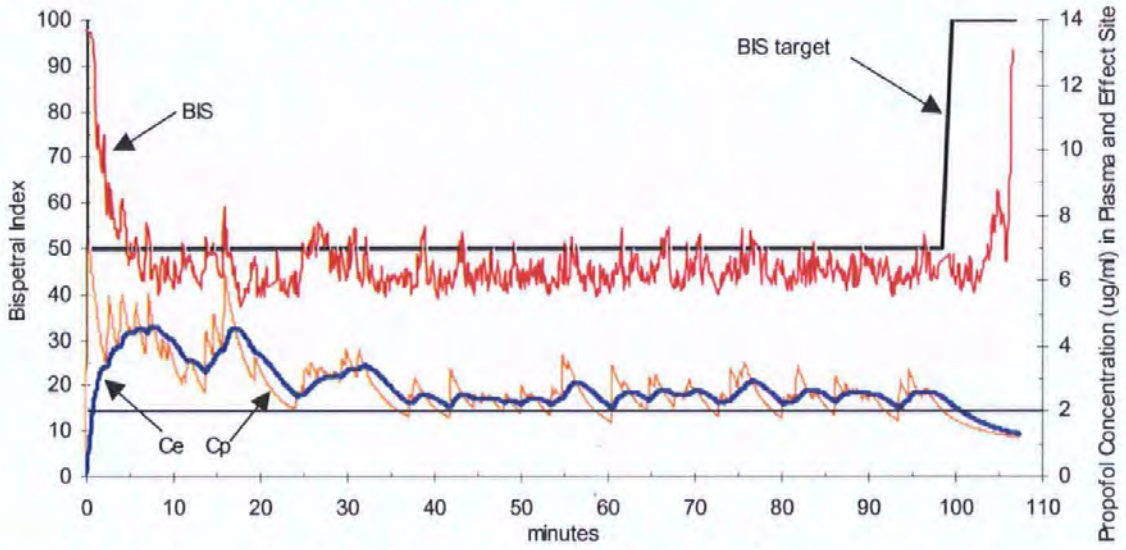


Figure 7-20 Expected BIS, BIS target, and predicted propofol concentration in plasma (Cp) and at effect site (Ce) in a single patient (patient 4) under total intravenous anaesthesia

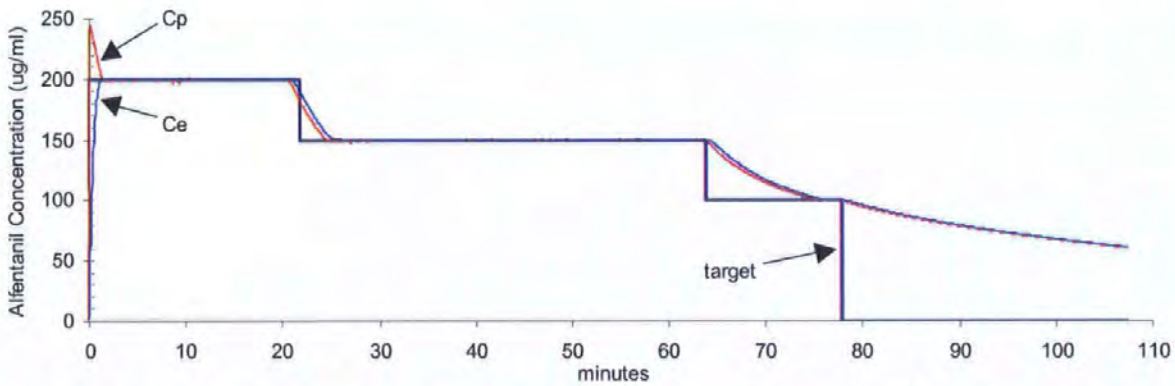


Figure 7-21 Predicted alfentanil concentration in plasma (Cp) and at effect site (Ce) in the same patient as in Figure 7-20 (patient 4) under total intravenous anaesthesia

7.7.4. Discussion

In this study, the CLAN system was working in an entirely different clinical environment. This group of patients (and only this group amongst our clinical studies) have continuous afferent (i.e. into the brain) sensory input. This ranges from touch through to painful stimulation. The painful stimulation is not constant during the entire procedure. It is because of this painful stimulation that an analgesic (i.e. alfentanil in this study) is needed.

In this study, propofol and alfentanil were infused simultaneously. However, there is interaction between the two drugs when used together. The interaction was identified by Vuyk and colleagues (1995b) as synergistic. The presence of alfentanil or any increase of alfentanil concentration will non-linearly reduce the requirement of propofol concentration, and the decrease in alfentanil concentration will non-linearly increase the requirement of propofol concentration. This is true vice versa. They also found out through computer simulation that the optimal combination of alfentanil and propofol in general anaesthesia is 3.5 mcg/ml propofol concentration and 85 ng/ml alfentanil concentration. This combination would produce a satisfactory intra-operative anaesthesia and allow the shortest recovery (in 10 minutes for 50% of patients) according to the simulation. However, the presence or increase of concentration of one drug does not increase the concentration of the other drug, and vice versa.

The following table (Table 7-19) shows the infusion control performance from the CLAN system in all four clinical studies.

Table 7-19 Control performance of CLAN system in all studies

	Study 1 Volunteers	**Study 2 Volunteers (N_2O)**	**Study 3 Knee surgery (epidural)**	**Study 4 Back surgery (alfentanil TCI)**
Induction Time (min)	3.2(1.4)	5.6(1.3)	7.8(1.9)	3.04(1.8)
Maintenance BIS	63.9(8.7)	62.7(6.5)	-3.6(10.9)**	-3.5(6.6)**
Maintenance Ce*	3.1(1.2)	3.5(1.0)	4.0(2.1)	4.3(1.3)
Recovery Time (min)	6.4(2.4)	5.9(1.6)	10.2(1.2)	12.02(2.5)
Wakening Ce*	1.3(0.4)	2.5(0.8)	1.91(0.8)	1.97(0.6)

*predicted propofol concentration at effect site, unit in mcg/ml **BIS error

With the presence of alfentanil, the CLAN system achieved the quickest induction of anaesthesia without significant overshoot and less BIS oscillation during the induction phase and shortly after. This is probably because of the drug interaction and the rapid onset of action of alfentanil, which speeded up the induction while the propofol concentration was building up. The predicted effect site concentration maintained in this study (4.3(1.3) mcg/ml) is higher than any previous studies because lower BIS targets (<=50) or deeper anaesthesia was required in surgeries under general anaesthesia. If we assume that the predicted propofol

concentration exceeds the measured concentration with a median absolute performance error (MDAPE) of 26% and a median performance error (MDPE) of 24% (Vuyk et al., 1995a), the real propofol concentration maintained in patients of this study would have been close to the optimal drug combination that gives propofol concentration of 3.5 mcg/ml (and 85 ng/ml for alfentanil). Towards the end of surgery, the alfentanil concentration was set to 80-100 ng/ml based upon the optimal combination to allow quick recovery. The recovery time 12.02(2.52) minutes in patients of this study is consistent with Vuyk and colleagues' simulation result (1995b) of 10 minutes when using optimal combination of propofol and alfentanil concentrations.

Although stronger and non-constant stimuli were present, there is a significant improvement in the control performance on BIS in this study over the previous patient study (-3.5(6.6) versus -3.6(10.9)). Unlike the previous patient study where all painful stimulation was cut off by the regional anaesthesia, the patients in this study received a (variable) nociceptive input.

A BIS rise in response to stimulation can be seen in the first and especially the third study. However, big changes in BIS were never seen in this study because of the maintenance of a deeper level of hypnosis (BIS target of 50), the presence of alfentanil, and improved CLAN system response speed. IselinChaves and colleagues (1998) reported that the absolute change of BIS after a painful stimulus was significantly decreased by both an increase in the concentration of propofol and the presence of alfentanil. Their finding was supported by this study in which there is no evidence of any significant BIS response to painful stimulation. When the requirement of propofol concentration for a certain level of anaesthetic depth is reduced due to the presence of alfentanil, the time needed to build such a reduced propofol concentration will be shorter. This actually increases the response speed of the CLAN system.

Before the start of this study, the CLAN system was modified to allow earlier response to any sudden BIS rise even when BIS value is under the target. This was implemented by the combined use of BIS prediction and BIS overshoot threshold value (-2.5), as described in Section 6.6.5.

This method was only used for detecting the time for the BIS to reach the overshoot threshold BIS value under the BIS target so that the CLAN system will turn on the infusion one cycle (5 seconds) earlier when BIS changes up from under the target.

By predicting the next BIS with a threshold BIS value, the CLAN system is able to respond to stimulation earlier, thus it potentially reduces the effect of hysteresis on infusion control.

However, as a result of this, the BIS will be maintained slightly under the target for the most of the infusion time as can be seen in this study. This is why the mean value of BIS in this study is 3.5 under the target. The use of this method and the presence of strong stimulation effectively engaged the infusion control throughout surgery and successfully avoided long time absence of infusion as seen in patients of previous studies.

When the BIS is maintained below or well below the BIS target and a painful stimulation happens, the patient could become responsive and consequently BIS would rise. As soon as the predicted BIS is above the threshold value the CLAN system resumes propofol infusion, or increases the infusion rate if the infusion has already started (when BIS is maintained between the target and the threshold value). The increase of propofol concentration will bring the patient into a deeper level of hypnosis, and it also reduces the requirement of alfentanil concentration that in return enhances the analgesic effect with unchanged alfentanil concentration. This way the BIS change in response to a painful stimulation is suppressed, and the sign of this stimulation is therefore buried into the normal BIS pattern of small oscillation.

In patient 4 (see Figure 7-20) for example, the measured BIS was maintained below the target almost throughout the surgery, and the propofol infusion was actively engaged due to the use of the BIS overshoot threshold value of -2.5, the BIS prediction mechanism, and the minimum effect site propofol concentration (2 mcg/ml). Due to the improvement of the CLAN system, no sudden big BIS jump was observed or recorded in any patients in this study.

Without the episodes of light anaesthesia, the CLAN system achieved the best result of all four clinical studies. The problem from the controller gains coping with the inter-patient variability did not show up because of this.

The quality of the electrode lead caused concern in this study. The CLAN system exited the infusion control in patient 5 and 6 because of the bad condition of leads from which bad quality of EEG signal was measured and this caused the wrong calculation of BIS in the anaesthesia monitor. This happened again on patient 8 and 9 as the patients awoke with body movement after the termination of infusion.

8. Discussions, Future Work and Conclusion

8.1. Discussions

Anaesthesia monitoring plays an important role in the operating theatre for surgery and in the intensive care unit. Traditionally, anaesthetists deliver anaesthetic drugs manually using their experience and clinical signs. Automation of anaesthesia monitoring would minimise the possibility of excessive dosing. Although TCI automates the drug administration, experienced anaesthetists are still required to adjust the target concentration. Closed-loop anaesthesia is superior to TCI technology and could lead to better patient care by intelligently controlling drug administration based on on-line monitoring of anaesthesia, and allowing prompt identification of and response to perturbations that might go unnoticed by a clinician.

This project has set out to investigate closed-loop anaesthesia for better patient care, and to develop a safe and reliable closed-loop anaesthesia system that could be used as a research tool in both intensive care unit and operating theatre.

The main contributions of the project include the development of a generic mathematic model of closed-loop anaesthesia, closed-loop controlled anaesthesia induction, system supervision techniques, and the development of a closed-loop anaesthesia system.

1. A generic mathematic model of closed-loop controlled anaesthesia which consists of the following sub-components:

    - PID Controller component model
    - Pharmacokinetic (PK) component model
    - Pharmacodynamic (PD) component model
    - Patient component model

    The mathematical model, which had not been reported at the time it was developed, can serve as a generalised tool for investigating closed loop anaesthesia. The model is modular and its sub-components can be readily updated or replaced. The mathematical model is developed as generally as possible and so can be used for various purposes. In this project, it was used for the investigation of the control strategy, for controller gain tuning, and for the investigations of patient variability in pharmacokinetics and pharmacodynamics.

By replacing the controller model, it can also be used for investigating other control strategies (e.g. fuzzy logic control and adaptive control) and evaluating their performance and tuning controller parameters. In future, the pharmacokinetic, pharmacodynamic, and patient models can be updated if there is significant advance in clinical understanding of CLAN. For example, in the project, the pharmacodynamic model specifies the relationship between propofol concentration and the drug effect (depth of anaesthesia) measured by Bispectral Index. However, other feedback signals that measure depth of anaesthesia could easily be accommodated by replacing the concentration-effect relationship algorithm. The patient component model allows testing of a closed-loop anaesthesia system with any control strategy on as many virtual patients as necessary and can be easily updated with more accurate pharmacokinetic parameters.

Due to the generalisation of the component model interface, the mathematical model provides an important entry point for investigation, design, implementation, and test of variety of closed-loop anaesthesia control systems using different control strategies and various feedback signals that measure depth of anaesthesia.

This work has resulted in a journal paper published in 2001(Sneyd, 2001).

2. Closed-loop controlled anaesthesia induction

Anaesthesia induction is a significant problem in anaesthesia monitoring because of inter-patient variability. Ideally, anaesthesia induction should have a rapid onset without overshoot for all patients. Traditionally, anaesthetists induce anaesthesia by giving a bolus infusion based on experience and pre-calculation of the bolus size, which is often at the cost of overshoot. However, multiple-bolus infusion schemes have been adopted for anaesthesia induction by some closed-loop anaesthesia control systems by increasing the open-loop target concentration step-by-step. In the CLAN system in this project, a closed-loop anaesthesia induction technique is developed. The CLAN system monitors the drug effect in individual patients and intelligently decides whether another bolus infusion is necessary during the next cycle and calculates the size of the bolus objectively based on the desired drug effect and that measured.

3. Controller compensation technique

A closed-loop anaesthesia control system is a safety critical feedback control system.

It requires fast response with minimum overshoot in patients with dynamic characteristics. The feedback signal is self-fluctuating with dynamic length of delay. Furthermore, there is no way to take infused drug out of the patient. These properties make a closed-loop anaesthesia system a non-linear dynamic system with delayed feedback signal.

To tackle problems inherent in closed-loop anaesthesia, a controller compensation (or supervision) technique, which is independent of controller type, was developed. This compensation technique or supervision system provides an intelligent solution for the problems caused by non-linearity, dynamics (such as varying hysteresis), and feedback delay. This technique also supports patient safety by monitoring the drug effect and infusion rate. Various digital signal processing algorithms have been developed for this mechanism.

4. Development of the CLAN system for total intravenous anaesthesia

The CLAN system developed is the first research system in this project that is capable of delivering both a hypnotics and an analgesic agent simultaneously, and the control strategy investigated in this project has never been previously reported. The CLAN system physically consists of two anaesthesia pumps, an EEG monitor, and a personal computer. Functionally, the system is composed of a PID controller, two TCI systems, a system control unit or a supervision system, and a user interface. The CLAN system was tested with a population of 78125 virtual patients based on the published data, and evaluated on healthy volunteers (n=21) and patients (n=15) undergoing surgery in various clinical environments. The anaesthesia quality maintained by the CLAN system is clinically satisfactory.

This CLAN system provides a platform for further investigations in closed-loop anaesthesia, patient variability in pharmacokinetics and pharmacodynamics, drug interaction, as well as leading towards systems for routine clinical use. Other control strategies such as fuzzy logic controller, neural network controller, or any other adaptive controllers can be easily evaluated on this platform.

This work has resulted in three conference abstracts (Dong et al., 1999a, 1999b, 1998).

8.2. Limitations and Future Work

The research on closed-loop anaesthesia is at a very early stage, and this investigation is a

new approach to the solution of this problem. The long-term objective of this project is to provide a basis for the development of a commercial CLAN system for total intravenous anaesthesia. To achieve this goal, there are a number of limitations to be addressed and overcome in the current investigation.

These limitations are discussed below together with proposals for future work on which a more advanced CLAN system could be based.

- **Lack of an adaptive controller**. As demonstrated by the computer simulations using the CLAN model and shown by the volunteer/patient studies, the same dose of initial bolus resulted in a wide range of drug concentration and effect in individual subjects. This patient variability would largely affect the drug infusion rate calculation. Clearly, for those who are more sensitive to a drug (i.e., same amount of drug results in higher drug concentration or more drug effect in them than in others, or vice versa), less drug should be infused in achieving and maintaining the target. This means that a smaller set of controller gains should be used. Therefore, an adaptive drug sensitivity model, which assesses and quantifies the drug sensitivity in individual subjects, should be developed in the future research. This sensitivity model should be dynamically updated throughout the drug infusion as it may change over time, and the controller gains should be adaptively adjusted against the individual drug sensitivity.

- **Lack of dynamic hysteresis analysis in individual patients**. Hysteresis of drug distribution is an important factor in drug infusion. The variations of drug effect peak time are clearly shown by the anaesthesia induction both in the investigation via computer simulation and in the clinical experiments. When inadequate anaesthesia, which is usually caused by stimulation, occurs, the controller usually gives a series of boluses. However it is unknown when drug infusion should be turned off without this information. For this reason, a BIS undershoot is frequently followed by a BIS overshoot in clinical experiments. In the future, a mechanism to detect this hysteresis in individual subjects should be developed. The quantification of individual hysteresis also helps the built-in pharmacokinetic model make a more precise estimation in effect site drug concentration.

- **Lack of a stimulation level model**. Another important factor that affects the drug infusion rate calculation is the stimulation level. Intuitively, higher stimulation level causes lighter anaesthesia level and hence more drug is required to re-achieve the drug

effect target. Practically, any occurrence of inadequate anaesthesia could be considered as the existence of stimulation with varying levels. Therefore a model that describes how much extra drug should be infused according to the stimulation level should be developed in the future.

- **Lack of analgesic effect monitoring**. Currently, a TCI system is used in this investigation to deliver analgesics due to the lack of an analgesic effect monitor. A closed-loop control system should be developed as soon as such a monitor is available.

- **Incomplete drug interaction investigation**. In this project, the interaction has only been investigated between propofol and alfentanil or nitrous oxide because of the time schedule. However, to achieve the commercial product goal in the long term, more combinations of drugs should be investigated.

- **Incomplete validation**. The prototype CLAN system has only been evaluated on healthy volunteers and ASA I/II patients. This does not cover all categories of patients, and therefore further validation is needed on a wider range of patients. A database holding all clinical data is highly recommended in favour of further investigations on patient variability (in both pharmacokinetics and pharmacodynamics) and drug interaction in the future.

- **Lack of a graphical user interface**. A friendly graphical user interface is essential for an interactive commercial product. The current user interface is based on DOS, and is only for research purposes. Graphical displays of variable histories are essential. These variables include drug concentrations in plasma and effect site and their targets, the drug effect (BIS in this investigation) and its target, drug infusion rate, and the amount of drug infused.

- **More control strategies need to be investigated**. This investigation uses a PID control strategy because of limited project time schedule and the simplicity and efficiency of PID controllers. However, the drug infusion process is highly complex and it contains too much uncertainty at this stage because of the limitations in the understanding of pharmacokinetics and pharmacodynamics, which result in incomplete modelling and substantial modelling errors. Fuzzy logic and neural network training, which are useful to solve the problems from incomplete modelling and uncertain dynamics, are good candidate control strategies for further investigation of closed-loop anaesthesia.

8.3. Conclusion

Closed-loop anaesthesia has been investigated in this project. Much of the work and effort over the course of this programme of work has gone into developing the mathematical CLAN model, investigating the problems in closed-loop anaesthesia by using the CLAN model, developing digital signal processing techniques to tackle the inherent problems (for example, the non-linear characteristics of the system, incomplete PK/PD modelling or uncertainty), and in developing a CLAN system delivering total intravenous anaesthesia. A working prototype has been developed with comprehensive patient safety protection mechanism. A robust test of the mathematical CLAN model has been carried out on 78125 virtual patients modelled by using published data, and the prototype system has been evaluated in typical clinical settings on 21 healthy volunteers and 15 patients undergoing surgery.

The novelty in this investigation is in the mathematical modelling of closed-loop anaesthesia process, the investigation of the control strategy of combining a PID controller with a pharmacokinetic model, the closed-loop anaesthesia induction scheme, system supervision scheme, and in providing a single integrated platform that is capable of delivering both hypnotic and analgesic agents simultaneously.

Appendix A Data Format Transmitted by A-1000 EEG Monitor

A.1 Processed EEG Data Packet and Variables

Table A-8-1 Artifact flags transmitted by A-1000 via raw EEG port

Bit#	Signal	Description
0	(unused)	
1	Out Of Range	Each sample is checked for values out of range (limit is +1 mV and -1 mV).
2	Bad Slope	The slew rate of the signal is too high.
3	(unused)	
4	Throw Away	A previous artifact has caused this second to be artifacted.
5	Suppressed	The standard deviation for the entire second is below a minimum value.
6	Start Up	The monitor has just started up. For the first few seconds there is an artifact.
7	Serial Bit Error	There is a checksum error in the EEG Data from the IPU.
8	Total Power Too Small	When the smoothed power in the band from 0.5 - 30 Hz goes below 1 μV rms, then spectral variables are considered to be noise.
9	Motion	A sudden change has occurred in the power of the band from 1 to 10 Hz.
10	Glitch	A sudden change has occurred in the power of the band from 20 to 45 Hz.
11	Positive Leadoff Clipping	The raw eeg has been out of range in the positive direction for 5 seconds.

12	Negative Leadoff Clipping	The raw eeg has been out of range in the negative direction for 5 seconds.
13	Positive Leadoff	The positive lead is disconnected from either the DSC or the patient.
14	Negative Leadoff	The negative lead is disconnected from either the DSC or the patient.
15	Clipping	The raw eeg data has been out of range during the last second, and the data has been clipped at the largest positive or negative value.
16	Framing Error	The current frame of data from the DSC is bad. This signal is polled at a 16Khz rate.
17	DSC Busy	The DSC cannot receive commands.
18	No DSC Interrupt	The DSC is not interrupting the IPU.
19	DSC Interface Error	The interface between the DSC and monitor is malfunctioning.
20	DSC Power Regulation Fault	The voltage regulators on the DSC are malfunctioning.
21	DSC Not Present	The DSC is disconnected from the monitor, or is not receiving power from the monitor.
22	DSC Overcurrent	The DSC is drawing too much current.
23	PLL Not Locked	The phase lock loop is not locked.
24	No DSC Status	This signal indicates that a status nibble from the DSC was requested but was not received.
25	Blocking	The DSC is in Blocking mode.

26	Negative Impedance Check	The DSC is checking the impedance of the negative lead.
27	Start Up	The DSC is in the process of turning on.
28	Software Error	Error detected in the serial interface between FPU and IPU, error detected In timing from DSC, or error detected in processing overrun
29	Positive Impedance Check	The DSC is checking the impedance of the positive lead.
30	(unused)	
31	(unused)	

Table A-8-2 Processed variables transmitted by A-1000 via raw EEG port

Variable Name	**Description**	**Range**
Bispectral Signal Quality (SQI)	The percentage of good epochs and suppressed epochs in the last 120 (61.5 seconds) that could be used in the Bispectral Index calculation.	0.0 - 100.0 %
Power Spectrum Signal Quality (PSQI)	The percentage of good epochs in the last spectral smoothing period.	0.0 - 100.0 %
Suppression Ratio Signal Quality (BSRSQI)	The percentage of good seconds in the last 63 seconds	0.0 - 100.0 %
Asymmetry Signal	The percentage of good epochs in the last	0.0 - 100.0 %

Quality (ASYSQI)	spectral smoothing period.	
Absolute Delta Power (ADELTA)	A measure of the power in the Delta frequency range (0.5 to 3.75 Hz).	40.0 - 100.0 dB
Absolute Theta Power (ATHETA)	A measure of the power in the Theta frequency range (4.0 to 7.75 Hz).	40.0 - 100.0 dB
Absolute Alpha Power (AALPHA)	A measure of the power in the Alpha frequency range (8.0 to 13.5 Hz).	40.0 - 100.0 dB
Absolute Beta Power (ABETA)	A measure of the power in the Beta frequency range (13.75 to 30.0 Hz).	40.0 - 100.0 dB
Total Power (TOTPOW)	A measure of the absolute total power in the frequency range from 0.5 to 30.0 Hz.	40.0 - 100.0 dB
User Band 1 Power (PBI)	A measure of the absolute power in the frequency range defined by the User Band 1.	40.0 - 100.0 dB
User Band 2 Power (PBII)	A measure of the absolute power in the frequency range defined by the User Band 2.	40.0 - 100.0 dB
Relative Delta Power (RDELTA)	The percentage of the Total Power which lies in the Delta frequency range.	0.0 - 100.0 %
Relative Theta Power (RTHETA)	The percentage of the Total Power which lies in the Theta frequency range.	0.0 - 100.0 %
Relative Alpha Power (RALPHA)	The percentage of the Total Power which lies in the Alpha frequency range.	0.0 - 100.0 %
Relative Beta Power (RBETA)	The percentage of the Total Power which lies in the Beta frequency range.	0.0 - 100.0 %
User Band Ratio (PBRAT)	The ratio formed by User Band 1 Power divided by User Band 2 Power, reported as a percentage.	0.0 - 100.0 %
Suppression Ratio (SR)	The percentage of epochs in the past 63	0.0 - 100.0 %

	seconds in which the EEG signal is considered suppressed.	
Spectral Edge Frequency (SEF)	The frequency at which 95% of the total power lies below it.	0.50 - 30.00 Hz
Median Frequency (MEDFRQ)	The frequency at which 50% of the total power lies below it.	0.50 - 30.00 Hz
Asymmetry Value (ASYM)	The ratio of the total power in channel 1 (or channel 3) to the sum of the total powers of channels 1&2 (or channels 3&4).	0.0 - 100.0 %
Bispectral Index (B30U)	This variable gives a bispectral index.	0.0 - 100.0
Bispectral Index (B31U, displayed as BIS)	This variable gives a bispectral index.	0.0 - 100.0
Bispectral Index (B31F)	This variable gives a bispectral index.	0.0 - 100.0
EMG Band 1 (EMGLOW)	The absolute power in the 70 - 300 Hz range.	0.0 - 100.0 dB
EMG Band 2 (EMGHI)	The absolute power in the 70 - 110 Hz range.	0.0 - 100.0 dB

The processed EEG variables are transmitted in ASCII format in the format and order shown below followed by a sample data record. The value of a variable is sent by using 8 ASCII characters separated by a vertical bar '|'.

```
Time            |Update
|SpSmooth|BiSmooth|LoFilter|NotFiltr|HiFilter|SpecArtf|BisArtf |
ADELTA  |ATHETA  |AALPHA  |ABETA   |TOTPOW  |PBI     |PBII    |RDELTA  |RTHETA
|RALPHA  |
RBETA   |PBRAT   |SR      |SEF     |MEDFRQ  |ASYM    |B30U    |B31U    |B31F
|EMGHI   |
EMGLOW  |SQI     |ASYSQI  |PSQI    |BSRSQI  |ARTF    |ADELTA  |ATHETA  |AALPHA
|ABETA   |
TOTPOW  |PBI     |PBII    |RDELTA  |RTHETA  |RALPHA  |RBETA   |PBRAT   |SR      |SEF
|
MEDFRQ  |ASYM    |B30U    |B31U    |B31F    |EMGHI   |EMGLOW  |SQI     |ASYSQI  |PSQI
|
```

```
BSRSQI  |ARTF    |ADELTA  |ATHETA  |AALPHA  |ABETA   |TOTPOW  |PBI     |PBII
|RDELTA  |
RTHETA  |RALPHA  |RBETA   |PBRAT   |SR      |SEF     |MEDFRQ  |ASYM    |B30U    |B31U
|
B31F    |EMGHI   |EMGLOW  |SQI     |ASYSQI  |PSQI    |BSRSQI  |ARTF    |ADELTA
|ATHETA  |
AALPHA  |ABETA   |TOTPOW  |PBI     |PBII    |RDELTA  |RTHETA  |RALPHA  |RBETA
|PBRAT   |
SR      |SEF     |MEDFRQ  |ASYM    |B30U    |B31U    |B31F    |EMGHI   |EMGLOW  |SQI
|
ASYSQI  |PSQI    |BSRSQI  |ARTF    |ADELTA  |ATHETA  |AALPHA  |ABETA   |TOTPOW  |PBI
|
PBII    |RDELTA  |RTHETA  |RALPHA  |RBETA   |PBRAT   |SR      |SEF     |MEDFRQ  |ASYM
|
B30U    |B31U    |B31F    |EMGHI   |EMGLOW  |SQI     |ASYSQI  |PSQI    |BSRSQI  |ARTF
|
ADELTA  |ATHETA  |AALPHA  |ABETA   |TOTPOW  |PBI     |PBII    |RDELTA  |RTHETA
|RALPHA  |
RBETA   |PBRAT   |SR      |SEF     |MEDFRQ  |ASYM    |B30U    |B31U    |B31F
|EMGHI   |
EMGLOW  |SQI     |ASYSQI  |PSQI    |BSRSQI  |ARTF    <CR><LF>
```

A sample data record:

```
01/30/1998 11:37:01
  10s      OFF      OFF 2.00 Hz    50 Hz     30 Hz FFFFF9FF FFFFFFFF
60.85    57.96    53.31    48.22    63.27     44.67    63.43     57.3     29.5     10.1
  3.1      1.3   6430.6    11.00     3.00      43.9   6430.6   6430.6   6430.6   586.33
86.14      0.0      0.0      0.0      0.0 0FA49000
62.85    57.86    50.55    47.95    64.34     34.30    64.35     71.0     22.5      4.2
  2.3      0.1   6430.6     9.00     2.50      43.9   6430.6   6430.6   6430.6   588.81
588.94     0.0      0.0      0.0      0.0 0FA49000
  0.00     0.00     0.00     0.00     0.00      0.00     0.00      0.0      0.0      0.0
   0.0    200.0   6430.6    30.00    30.00      50.0   6430.6   6430.6   6430.6   585.80
587.09     0.0      0.0      0.0      0.0 0FA49100
  0.00     0.00     0.00     0.00     0.00      0.00     0.00      0.0      0.0      0.0
   0.0    200.0   6430.6    30.00    30.00      50.0   6430.6   6430.6   6430.6   587.44
587.34     0.0      0.0      0.0      0.0 0FA49100
 61.85    57.91    51.93    48.09    63.80     39.48    63.89     64.2     26.0      7.1
   2.7      0.7   6430.6    10.00     2.75      43.9   6430.6   6430.6   6430.6   587.57
587.54     0.0      0.0      0.0      0.0 0FA49000
  0.00     0.00     0.00     0.00     0.00      0.00     0.00      0.0      0.0      0.0
   0.0    200.0   6430.6    30.00    30.00      50.0   6430.6   6430.6   6430.6   586.62
587.22     0.0      0.0      0.0      0.0 0FA49100

ERROR   |01/30/1998 11:37:01|DSC Disconnected (E01)
ERROR   |01/30/1998 11:37:01|Poor Signal Quality (E43)
IMPEDNCE|01/30/1998 11:37:01|-    800|-   1300|-      0|-      0
```

A.2 Raw EEG Data Packet

The raw EEG data packet is transmitted sequentially in binary format, and the order of data transmission is in the sequence described in Table A-8-3.

Table A-8-3 Raw EEG packet - 128 samples/second

Header (byte) = 0xab
Type (byte) = 2
Sequence Number (16 bits)
Raw EEG data, 4 channels interleaved
Checksum (16 bits)

There are 4 data channels in total. The data in each channel is from the measurement of EEG waveform from a dedicated electrode lead attached to patients. The data from the four channels are interleaved when transmitted, i.e., in the order of Ch1->Ch2->Ch3->Ch4->Ch1.

Appendix B Clinical Data Archiving

B.1 File Structure

There is a directory structure for storing the clinical data collected from the patient studies. The data include raw EEG data, processed EEG variables, extracted BIS data, calculated drug concentration in plasma and at effect site, infusion rates, and volume of drug infused at each interval (5 seconds). To avoid over large of the data files, the incoming data are split into sections and stored in files under the dedicated directories according to the type of the data. Each raw EEG data file contains only five minutes data, each processed EEG data file contains the data of fifteen minutes while BIS file contains two hours data because of the low data rate. A data archive directory structure has been built for this purpose, which is shown below:

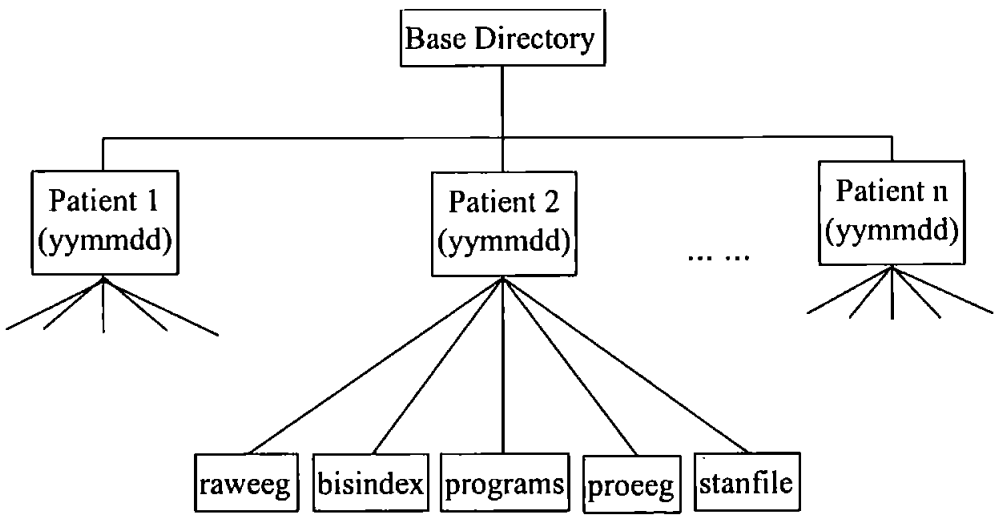


Figure B-8-1 Data archiving structure

The base directory is the one in which the system executable resides. The data of a specific patient are stored in a dedicated directory. The patient directory name is made up of the year (yy), month (mm), and date (dd) of the study. Each patient directory consists of 5 subdirectories storing raw EEG data, processed EEG data, BIS data, drug related data (such as drug concentration, infusion rate, etc.), and the programs used for the study. If the programs directory is empty, it indicates that the last version of the programs were used. The name of individual BIS, raw EEG, processed EEG data file uses the naming convention of mmddhhmm.ext which is similar to the naming of the patient directory. The extension name

for BIS data file is .bis, for raw EEG data is .raw, while .pro for processed EEG data.

The file Log.txt and Personal.txt under the patient directory contain the patient information. While Log.txt contains the public data and any event occurs during the study, the Personal.txt contains the private data of the patient and is not allowed to be public accessible.

Note: Each raw EEG data packet is stamped by the data logger with the time of receipt at the head.

Table B-1 Trial names and directory names of the clinical experimental data

Trial Names	Trial101	Trial102	Trial103	Trial104	Trial105	Trial106
Dir Names	980122.101	980130.102	980206.103	980214.104	980226.105	980226.106
Trial Names	Trial107	Trial108	Trial109	Trial110	Trial111	Trial112
Dir Names	980227.107	980323.108	980402.109	980417.110	980420.111	980423.112
Trial Names	Trial113	Trial201	Trial202	Trial203	Trial204	Trial205
Dir Names	980423.113	980731.201	980904.202	980911.203	980918.204	981002.205

B.2 File Locations

The full clinical trial data are stored both on PC and network server in both the University and Derriford Hospital with a hard copy stored in a CDROM. Following are the path of the archiving:

University of Plymouth:

D:\TCI\Trials (PC, Apricot LS550)

/lisbon/staff/chao/CLAN Data (server)

Derriford Hospital:

C:\TCI\Trials (PC, Compaq Desktop, serial number A3778)

/Phtserver04/Dongc/CLAN Data/ (server)

Appendix C Run-Time Command File

The CLAN system developed has a long list of command line options to initialise the system, such as selection of a specific drug, type of anaesthesia pump, syringe size, patient data, system parameters, and so forth. In order to avoid the on-line input of these data in which some of them are fixed in this investigation, a command file cmd_file.txt is designed and used for this purpose. The typical options available in the command file is shown below (options are in bold font type and the value of the options are in regular font type:

```
START_SETTING
*basic_settings:
      Graseby user username  delta 5 quick delete   *debug   *io_display
      direct_control 0  working_mode 5  fixed_model  1
*patient_data:
      file filename subject patient_name initials x
      height 180 weight 70  gender male age 50
      hospital_number xxxxxxxx  DOB xx/xx/xxxx
*simulation_data:
      PKPD    1            t_peak    2.3           V1    0.159
      k10     0.152 k12    0.207     k13   0.04
      k21     0.092 k31    0.0048    ke0   0.25
      start_simu_time      20        end_simu_time       3000
      target_change_time1  1200      target_change_time2 2400
      second_target        50        third_target        65
*simulation_patient_control:
      use_converted_BIS      0
      pseudo_bis_from_file   0
*targets:
      target effect *plasma propofol gepts
      BIS_target 65          desired_initial_bolus -2.22   max_cp  10.0
      upper_limit   1.5      lower_limit   -2.5
*PID_gains:
      kp_ic    0.0024  ki_ic    0.00001    kd_ic   0.169
END_SETTING
```

The command file includes five parts, which are basic_settings, patient_data, simulation_data, targets, and PID_gains. The valid command starts from the unique word START_SETTING, and ends with the unique word END_SETTING. The words in bold type are commands, and the rest of them are parameters needed by the commands.

The meanings of the commands are listed below, where [TCI] is followed, the command is inherited from STANPUMP:

A1000_Ver : followed by 330 or 312 for BIS algorithm version 3.30 or 3.12
Graseby: if this command appears in the command file, the system will run with two pumps, otherwise no pump involves. No parameter is followed after this command. [TCI]
user: followed by the name of the user. [TCI]
delta: followed by the system update cycle, or the sampling period. [TCI]
quick: speed up the initialisation. [TCI]
delete: if the study file name already exists, delete the old file. [TCI]
debug: enable the display of debug information in the run time. [TCI]

io_display: enable the display of I/O status. [TCI]
direct_control: 1 for non-model based PID control (not implemented)
0 for indirect PID control via a PKPD model.
working_mode: the parameter followed is now always 5.
fixed_model : 1 - use fixed PKPD model
0 - use adaptive PKPD model (not implemented)
file: followed by the study file name [TCI]
subject: followed by the patient name [TCI]
initials : followed by the initials of the patient [TCI]
height : followed by the height of the patient [TCI]
weight : followed by the height of the patient [TCI]
gender : followed by the gender of the patient [TCI]
age : followed by the age of the patient [TCI]
hospital_number : followed by the hospital number of the patient (optional)
DOB : followed by the date of birth of the patient [TCI]
PKPD : 1~9, user defined PKPD parameter sets for propofol, refer to the code in drug.c. if PKPD=10, the following PKPD parameter set specified in V1, k10, k12, k13, k21, k31, ke0 will be used for the simulation.
start_simu_time : the start time of infusion in simulation
end_simu_time : the end time of infusion in simulation
target_change_time1: the time of the first change of the BIS target
target_change_time2 : the time of the second change of the BIS target
second_target : the second target applied at the first BIS target change time
third_target : the third target applied at the second BIS target change time
use_converted_BIS : 1(0) - the BIS converted from Ce will (not) be used
pseudo_bis_from_file : 1(0) - the BIS read from an external file will (not) be used

BIS_target : the initial BIS target
target : use target controlled infusion instead of bolus infusion
propofol : followed by the name of the propofol PKPD parameter set
propofol_effect : target on effect site for propofol
propofol_plasma : target on plasma for propofol
alfentanil : followed by the name of the alfentanil PKPD parameter set
alfentanil_effect : target on effect site for alfentanil
alfentanil_plasma : target on plasma for alfentanil
propofol_target: the effect site drug concentration to be used for calculating the initial bolus. If the concentration is positive, then the system will give a bolus based on this value, otherwise the bolus will be given based on the initial BIS target.
alfentanil_target : followed by the alfentanil target concentration at effect site
max_ propofol _ce : the maximum propofol effect site concentration allowed
min_propofol_ce : the minimum propofol effect site concentration to be maintained
max_alfentanil_ce : the maximum alfentanil effect site concentration allowed
min_alfentanil_ce : the minimum alfentanil effect site concentration to be maintained
upper_limit : the threshold value of BIS to toggle the propofol target on effect site
lower_limit : the threshold value of BIS to restart the PID control from overshoot
kp_ic : PID gain Kp
ki_ic : PID gain Ki
kd_ic : PID gain Kd

Appendix D CLAN System Hardware Settings

There is a distinct difference in the settings of CLAN system hardware components between that used for propofol sedation studies (two volunteer studies and the study with patients undergoing knee surgery) and that used for the total intravenous anaesthesia study with patients undergoing back surgery.

BIS algorithm v3.12 in Aspect A-1000 Monitor was used for the first three studies, while it was updated to BIS v3.30 for the last study.

Hardware settings for the first three studies (propofol sedation):

Aspect A-1000 monitor settings

- EEG channels : two channels bipolar
- Channel 1 : positive (Fp1), negative (F7)
- Channel 2 : positive (Fp2), negative (F8)
- Reference (ground) : Fpz
- Spectral smoothing : OFF
- Bispectral smoothing : OFF
- EEG Filtering : Low – 2 Hz, High – 30 Hz
- EEG sweep speed : 25 mm/s
- EEG scale : 25 uv/div
- Electrode lead-off detection : on
- Audible alarm : off
- BIS algorithm : v3.12
- EEG variable update rate : 5 seconds

Communication ports

- COM1 : processed EEG variables in ASCII format
- COM2 : raw EEG data in binary format
- COM3 : N/C
- COM4 : Graseby anaesthesia pump for propofol

Hardware settings for the last study (total intravenous anaesthesia):

Aspect A-1000 monitor settings

- EEG channels : two channels bipolar
- Channel 1 : positive (Fp1), negative (F7)
- Channel 2 : positive (Fp2), negative (F8)
- Reference (ground) : Fpz
- Spectral smoothing : OFF
- Bispectral smoothing : 15 seconds
- EEG Filtering : Low – 2 Hz, High – 70 Hz
- EEG sweep speed : 25 mm/s
- EEG scale : 25 uv/div
- Electrode lead-off detection : ON
- Audible alarm : OFF
- BIS algorithm : v3.30
- EEG variable update rate : 5 seconds

Communication ports

- COM1 : Graseby anaesthesia pump for alfentanil
- COM2 : processed EEG variables in ASCII format
- COM3 : raw EEG data in binary format
- COM4 : Graseby anaesthesia pump for propofol

Appendix E User Interface

E.1 Screen Messages

A Sample Run Time Screen Shot

Department of Anaesthesia Derriford Hospital Plymouth
Graseby 3400

Drug: Propofol Parameters: Gepts

7/10/1998 Day 01 15:20:00 Elapsed Time: 3min 40sec Aspect Time: 15:20:09

Pump Status: OK

Patient : J.Peters

Effect site level of 0.50 expected in 14.7 minutes

data not saved drive C: 128MB left

Channel 1:

Lead(+) Lead(-) ADELTA ATHETA AALPHA ABETA TOTPOW SEF MEDFRQ EMGHI EMGLOW

off 0.0 0.0 0.0 0.0 0.0 30.0 30.0 80.15 77.64

Channel 2:

Lead(+) Lead(-) ADELTA ATHETA AALPHA ABETA TOTPOW SEF MEDFRQ EMGHI EMGLOW

off 0.0 0.0 0.0 0.0 0.0 30.0 30.0 80.15 77.64

Location Units Predicted Target CH1 CH2 CH5 Feedback

Plasma mcg/ml 2.2261 2.2261
Good BIS

Effect Site mcg/ml 2.2272 -
0.00001

Bispectral Index 65.00 65.00 63.0 67.0 65.0
65.0

Infusion Rate: 5.16 ml/hour , 86.00 ug/kg/min Total Infused:
1.964 ml

F1: Change BIS target F8: Open-Loop Control

F2: Change lower threshold value(-2.5) F9: Pause infusion

F3: Change syringe F10: Terminate infusion at end of study

F11: Change gains(0.0024, 1e-05, 0.18) F12: Change max_Ce(10mcg/ml)

>1 10:10:10 000 Program start(Press ^F5 to toggle data save and event record)

^F1: last event ^F2: next event ^F3: even No
^F4: debug

^F5: save ^F6: make comment ^F7:
redraw screen

E.2 Command Menu

The interactive user interface of the system enables the user to start, pause, resume, and end the drug infusion at any time without losing data. Some system parameters can be modified on-line from the command menu. If BIS value is not available the system will automatically switch from closed-loop control to open-loop control, however, if the BIS value is not correct then the user is allowed to force the system to run in open-loop control. Target change can be made in both the closed-loop mode and the open-loop mode. Following is a list of the on-line commands available to the user:

F1 : change target BIS (closed-loop) or target concentration (open-loop)
F2 : toggle closed-loop and open-loop control
F3 : change syringe (either propofol or alfentanil)

F4 : start the infusion/change parameters (PID gains, threshold values, maximum and minimum propofol or alfentanil concentration)
F5 : pause/resume drug infusion (either propofol or alfentanil)
F6 : exit
^F1: view last event logged
^F2: view next event logged
^F3: view a specified event
^F4: display debug information
^F5: toggle data saving and event logging
^F6: make an event/comment or cancel the event/comment being made
^F7: redraw the screen

Appendix F List of Programs Developed

F.1 C Programs

The software of the CLAN system is written in C and runs in DOS. The following is a list of the C programs developed with description. For more details, please refer to the actual code.

stan2.c : this is a largely modified version of shareware STANPUMP main program. Update of two PKPD models (propofol and alfentanil), calculation of infusion rates for the two drugs, most of the security control are implemented in this program.

cmd2.c : part of STANPUMP, largely modified. Load the system variables from the command file.

async2.c: part of STANPUMP, modified. Part of pump driver

drugs2.c: definitions of various PKPD models for a number of drugs.

cube.c : part of STANPUMP, no modification. Solve characteristic equation.

drivers2.c : part of STANPUMP, modified. Part of pump driver.

gr_34002.c: part of STANPUMP, modified. Graseby 3400 pump driver.

keyboard.c: part of STANPUMP, no modification. Keyboard handler.

control.c : implementation of the PID controller and some rules.

tci.c : data logger main program

aspect.c : definitions of variables and functions used by the data logger

aspcfg.c : general functions used by the data logger

ascproeeg.c : functions for processed EEG data collection from processed EEG port

binproeeg.c : functions for processed EEG data collection from raw EEG port

raweeg.c : functions for collecting raw EEG data

kbdhandler.c : keyboard handler for data logger

All above programs are in d:\clan\simo\ at the university site, and c:\dongc\simo\ in the hospital.

EEG2SMR : c program to convert the raw or processed EEG data file into .smr file format which can be read by Spike 2 for Windows for post analysis. (d:\clan\eeg2smr\)

NB: 1. The programs listed above are for both the real system that can be used in a clinical setting, and the real time simulation system without using any pumps. If compile and build the project in IDE with RealTime=true in TCIpub.h, then a system that could be used with patient will be generated, otherwise a simulation system will be built.

2. All C programs were written for Borland C++ compiler, and were compiled and built in Borland C++ 5.0 or 5.02 IDE. To compile and build the CLAN system, the Greenleaf Comm Library is needed. For a Borland IDE project with target of standard DOS huge memory model, the gclh.lib should be included in the project. This library file is under \gcl520\B50\. For more details about this, please refer to the Greenleaf Comm Library manual.

3. There is a stand-alone version of data logger in d:\clan\aspect\ that runs with A-1000 to collect data only.

4. Also, a closed-loop controlled propofol only infusion system can be found in d:\clan\tci (university), c:\tci (hospital), and the CDROM under \clan\tci\. This is the previous version of the system with which three patient studies including 27 healthy volunteers/patients have been done.

F.2 MATLAB Programs

Matlab programs are for off-line simulation of the CLAN system, all Matlab programs are located in d:/clan/simu/matlab/ on the PC or the same path in CDROM.

The following is a list of the matlab programs:

Clan.m : the implementation of the CLAN system with TCI in Matlab.

Clanloop.m : a special version of Clan.m that runs the system for a specified number of times. Each time, the system runs with a different PKPD model.

Clanplot.m : plot the results obtained from Clanloop.m

MeanSD.m : calculate the means and standard deviations on the data obtained from Clanloop.m

TCI.m: an open-loop controlled simulation system, or implementation of TCI CONTROL in Matlab

New_ke0.m : a function to correct ke0 value with given peak time, called by Clan.m and TCI.m

Beforaft.m : a function performing numerical searching in determining the peak time, called by new_ke0.m

Findpeak.m: a function to find the time of peak effect after drug has been given, called by Clan.m and TCI.m

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Publications

Table 2 Loss rates of propofol from tissue samples

Tissue	Log (conc) per day		Loss rate (% per day)		Half life (days)
	Mean	SE	Estimate	95% CI	
Bolus: non-spleen	−0.001273	0.000161	0.293	0.22 to 0.37	236
spleen	0.000342	0.000263	−0.079	−0.20 to 0.04	−881
Infusion: all tissues	−0.000119	0.000150	0.027	−0.04 to 0.10	2525

Conc, concentration in $\mu g\ g^{-1}$; CI, confidence interval.

to the tissue concentration measurements to determine the fitted concentration at "day 0" – except that zero loss rate was used instead of the two non-significant loss rates. In the infusion experiments, the day 0 concentrations were divided by the fitted arterial concentration at the time of cardiac arrest to yield tissue/blood partition coefficients.

One possible mechanism of loss is evaporation. If that were the case, half life should be proportional to the solubility of propofol in the tissues; but there was nothing exceptional about spleen in terms of concentration in the bolus experiments or partition coefficient in the infusion experiments. Also it seems inconceivable that solubility in tissues in the infusion experiments was 10 times that in the bolus experiments. Another possibility is degradation of the propofol. There is wide overlap of concentrations of propofol between the three conditions in table 2, but the amount of its vehicle, Intralipid, would be much greater in the infusion experiments, and somewhat greater in spleen than other tissues because of the very high blood content of spleen. Could Intralipid have some kind of preservative action? Comments and alternative explanations will be welcomed.

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Keywords: anaesthetics i.v., propofol; sheep

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Closed loop computer controlled sedation with propofol

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Automated control systems are widely used in critical applications; however, their use in medical care is relatively unusual. We have developed a system for automatic control of sedation and tested it in seven human volunteers.

Bifrontal raw electroencephalogram (EEG) and derivatives including the bispectral index (BIS V3.12) were recorded and logged using an Aspect A1000 monitor and a personal computer with custom written software (C Borland). A proportional integral derivative (PID) controller and a four-compartment pharmacokinetic/pharmacodynamic (PK/PD) model automatically adjusted target effect site propofol concentration by controlling an infusion pump (Graseby 3400) to maintain a constant value of BIS. After a 10 minute baseline EEG recording without sedation, the BIS target was set to 65 for a period of 25 minutes, after which sedation was discontinued. "Open loop" target controlled infusion was used for the first 2.3 minutes. The initial target effect site propofol concentration (Ce) was calculated from the BIS target using the following formula adapted from Doi and colleagues[1]: $BIS = -12.837Ce + 93.582$.

Subsequently the PID controller adjusted the effect site target automatically—that is, a "closed loop." After 15 minutes of sedation subjects were stimulated with a nerve stimulator applied to the wrist (30 mA for 2 min followed by 40 mA for 3 min). Satisfactory sedation was achieved in all subjects (fig 1).

Attainment of the BIS target was rapid but three subjects were initially oversedated (minimum BIS values during minutes 0–5 for these subjects were 48.3, 34.9, and 41.5). The measured BIS in seven subjects between 2.3 and 15 minutes ("closed loop" control, no stimulation) was 65.2 (5.8) (mean (SD)), and between 15 and 20 minutes (during stimulation), 66.3 (6.8).

Our system automatically established and maintained sedation in volunteers. Clinical application will require further evaluation in patients.

Keywords: anaesthetics i.v., propofol; model, computer

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We thank Graseby Medical Ltd for the loan of an infusion pump and Dr Steven Shafer for some source C code from STANPUMP.

Reference

1. Doi M, Gajraj RJ, Manzaridis H, Kenny GNC. *British Journal of Anaesthesia* 1997; 78: 180–184.

A comparison of vasoactivity between levobupivacaine and bupivacaine

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Stereoisomerism and drug concentration both influence the vasoactive properties of local anaesthetic agents. Determination of

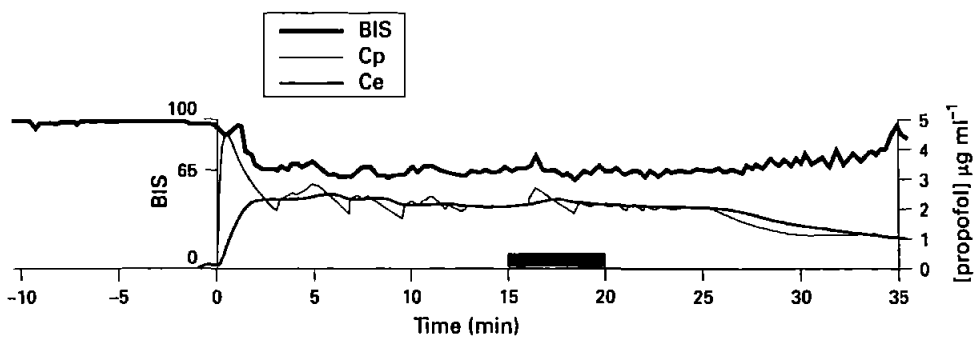

Figure 1 Bispectral index (BIS), predicted plasma propofol concentration (Cp), and effect site propofol concentration (Ce) in a single subject. The period of stimulation is indicated by a bar.

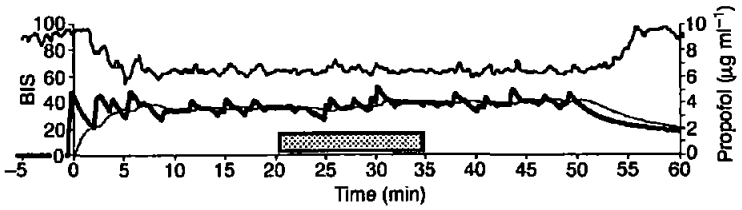

Fig 4 Bispectral index (BIS) (top curve), predicted plasma concentration (bottom thick curve) and predicted effect-site propofol concentration (bottom thin curve) in a single subject. Nitrous oxide was inhaled during the period indicated by the bar.

before and after intubation were derived, enabling measurement of Pa amplitude. Analysis of variance and Student's *t* test were used to compare the log-transformed data from these two periods for the saline, esmolol and alfentanil groups. Haemodynamic variables measured 1 min before and 1 and 5 min after intubation were subjected to similar statistical analysis but without log transformation.

The results are summarized in Table 3. Both esmolol and alfentanil blocked the AER response to intubation to the extent that the AER changes were not significantly different from zero. This has been reported previously for alfentanil[2] and may be explained by its analgesic effects. The attenuation produced by esmolol is in keeping with an anaesthetic sparing effect[1] and a central mechanism for this effect has to be considered.

Keywords: monitoring, evoked potentials; pharmacology, esmolol; sympathetic nervous system, esmolol; analgesics opioid, remifentanil; cardiovascular system, effects

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1 Johansen JW, Flaishon R, Sebel PS, *et al. Anesthesiology* 1997; **86**: 364–71
2 Shinner G, Sharpe RM, Shannon C, Thornton C, Dore CJ, Brunner MD. *Br J Anaesth* 1997; **79**: 137–8P

Does nitrous oxide affect closed-loop anaesthetic propofol?

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We have described previously closed-loop infusion of propofol using the bispectral index (BIS) and a feedback control system.[1] Nitrous oxide is used commonly as a supplement to propofol infusion to provide analgesia and additional hypnosis. We have evaluated introduction of nitrous oxide during closed-loop anaesthesia with propofol.

We studied eight volunteers (five males; aged 29–41 yr; weight 62–97 kg). An Aspect A1000 monitor recorded the raw EEG from bipolar leads (Fp1/Fp7 and Fp2/F8). BIS (V3.2) was obtained in real-time by the closed-loop control system running on a personal computer. Compared with the previous system,[1] the proportional integral derivative (PID) controller gains and supervision rule-base have been improved. Target concentration of the built-in PK/PD model was regulated by the controller while the target site (effect site or plasma) was regulated by the supervision rule-base.

After a 5-min baseline EEG recording, the BIS target was set constantly to 65 during the 50-min closed-loop propofol infusion. Subjects breathed 50% nitrous oxide between the 20th and 35th minutes.

Anaesthesia was achieved in all subjects. Two subjects were anaesthetized during induction with minimum BIS values of 42.4 and 46.9. After some initial instability, stable anaesthesia was achieved after a mean time of 7.6 (SD 3.5) min. Mean measured BIS between the time of establishment of stable anaesthesia and 20 min (propofol only) was 62.9 (3.7); between 20 and 35 min (propofol and nitrous oxide), 62.6 (5.4); and between 35 and 50 min (propofol only), 62.6 (8.4). Addition of nitrous oxide did not prevent maintenance of the anaesthesia target, but its withdrawal was associated with moderate oscillation of BIS in three subjects (Fig. 4).

Our closed-loop system maintained anaesthesia during and after addition of nitrous oxide in volunteer subjects who were not subjected to painful stimulation.

Keywords: sedation; anaesthetics i.v., propofol; anaesthetics gases, nitrous oxide; monitoring, electroencephalography

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Graseby Medical Ltd loaned the infusion pump and Dr Shafer gave some STANPUMP code.

Reference

1 Dong C, Kehoe J, Henry J, *et al. Br J Anaesth* 1988; 81: 631P

Closed-loop sedation during knee surgery under epidural anaesthesia

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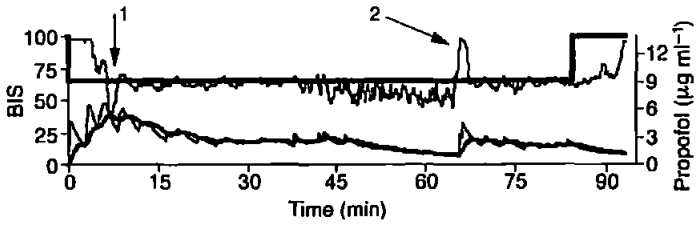

Fig 5 Bispectral index (BIS) (top thin curve) and its target (top thick curve), and predicted plasma (bottom thin curve) and effect-site (bottom thick curve) propofol concentrations in a single subject. After initial over-sedation (arrow 1), the closed-loop system established stable sedation. Between 45 and 65 min, BIS remained below the target and the controller allowed plasma propofol concentrations to decrease. The patient then 'awoke' (arrow 2).

We have reported previously computer-controlled closed-loop propofol sedation of volunteers.[1] We have subsequently evaluated this system in patients undergoing reconstructive knee surgery during epidural anaesthesia. A lumbar epidural catheter was placed under local anaesthesia either before (n=4) or after (n=2) starting sedation, and a regional block established. The BIS target was initially set at 65 and then adjusted at clinical discretion. Closed-loop sedation was maintained throughout surgery.

We studied six male patients (ASA I–II, aged 25–39 yr, weight 70–100 kg). One other patient was entered into the study but sedation was not commenced because of technical difficulties (broken cable). Sedation at the initial BIS target was established in a mean time of 7.8 (SD 1.9) min. Subsequently, the error between measured and target BIS in the six patients after induction was –3.4 (10.5). Changes in patient position and other stimuli during placement of the lumbar epidural catheter in the first four patients were associated with rapid changes in BIS and variable levels of consciousness. In two patients, during surgery, when stimulation was confined to the leg (i.e. blocked by the epidural), measured BIS remained slightly deeper than target. The controller therefore gradually reduced the target propofol concentration until the patient suddenly 'awakened' (Fig. 5).

Although the closed-loop system was initially able to induce and maintain sedation, the response of the proportional integral derivative (PID) controller to persistent small errors caused progressive withdrawal of the sedative agent which gave clinically unsatisfactory sedation in two patients. We hypothesize that this may have been caused by establishment of natural sleep.

Keywords: sedation; anaesthetics i.v., propofol; anaesthetics gases, nitrous oxide; surgery, orthopaedic

Acknowledgement
Graseby Medical Ltd loaned the infusion pump and Dr Shafer gave some STANPUMP code.

Reference

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Table 4 Times to reach 90% desaturation (Sa_{O_2}) using the METI system compared with those predicted by the model of Farmery and Roe.[1] The METI system was consistently slower than the model of Farmery and Roe

FRC (ml)	FI_{O_2}	Time for Sa_{O_2} to reach 90% (s)	
		METI	Farmery
1530	0.21	90	48
2700	0.21	145	64
4000	0.21	195	79
1530	1.0	240	161
2700	1.0	420	310
4000	1.0	590	430

Desaturation modelling in the 'human patient' simulator at the Bristol Medical Simulation Centre

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The Bristol Medical Simulation Centre uses a manikin and simulation software developed by Medical Education Technologies, Inc (METI). We investigated how realistically the METI system simulates normal physiology and chose to study one of the most fundamental emergencies in medicine—loss of airway and consequent interruption of the oxygen supply. We used the data-logging facility of METI to record the time course of decrease in arterial oxygen partial pressure (Pa_{O_2}) and oxyhaemoglobin saturation (Sa_{O_2}) after software imposition of 100% neuromuscular block. We did this at various settings of functional residual capacity (FRC) and fractional inspired concentration of oxygen (FI_{O_2}), at a fixed oxygen consumption ($\dot{V}_{O_2}$) of 250 ml min^{-1} and pulmonary venous admixture ('shunt', Qs/Qt) of 2%. We compared times to 90% Sa_{O_2} with those predicted by the model of Farmery and Roe.[1] The METI system was consistently slower than the model of Farmery and Roe (Table 4).

On further examination, the corresponding time courses of decreases in Pa_{O_2} were more closely aligned. Therefore, we examined for inconsistencies in the behaviour of the oxygen–haemoglobin dissociation curve using published standards.[2,3] We plotted the decrease in METI values of Sa_{O_2} with Pa_{O_2} at different values of steady state pH and

The Use of Simulations in Design of a Closed-Loop System for Computer Controlled Anaesthesia

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We are developing a closed-loop system for intravenous anaesthesia in human. Using published pharmacokinetic data for the intravenous anaesthetic agent, propofol, we have generated a population of "virtual patients" and simulated their response to induction and maintenance of intravenous anaesthesia using a feedback system based on an electroencephalogram (EEG) derivative. Our simulations suggested that the proposed system would accommodate patients with widely varying pharmacokinetic characteristics. The system was subsequently tested in human and successfully induced and maintained anaesthesia in seven volunteers.

KEYWORDS: anaesthesia; Bispectral Index; closed loop system; computer controlled anaesthesia; EEG; modelling; pharmacokinetics; pharmacodynamics; simulation; virtual patients.

In contrast to fields such as aviation, anaesthesia currently enjoys low levels of automation (Sharma et al., 1993; Glen, 1998). When an intravenous drug is used to induce and maintain anaesthesia, the doctor administering anaesthesia must estimate the initial dose and subsequently make an appropriate adjustment to the drug infusion rate in order to reflect the gradual accumulation of the drug within the body.

Recently, the introduction of Target Controlled Infusion (TCI) has made it easier to achieve relatively stable blood concentrations but the anaesthetist must still decide whether the patient's level of anaesthesia is sufficient and make adjustments as necessary (Glen, 1998). Electronic monitoring of the electroencephalogram (EEG) offers a selection of processed EEG derivatives which may reflect the patient's underlying state of anaesthesia. We are developing a closed-loop system for computer controlled anaesthesia in human using an EEG derivative, the Bispectral Index, as a feed back signal. Our work so far has involved extensive computer simulations using "virtual patients" and successful tests on volunteers after ethical approval.

We are grateful to Graseby Medical Ltd for the loan of an infusion pump and Dr Steven Shafer for some source C code from STANPUMP which formed a basis for the work. We are also indebted to the volunteers who made it possible to test system.

1. Feedback signal

The Bispectral Index (BIS) is a commercially developed EEG derivative optimised to produce a linear, monotonic index of hypnosis (depth of sleep/anaesthesia) (Doi et al., 1997; Leslie et al, 1995). The Bispectral Index (BIS) is a real-time EEG derivative generated by a proprietary algorithm developed by Aspect Medical Systems, Inc., and is a composite, numerical index ranging from 0 to 100 showing hypnotic states/sedation levels.

Before the calculation of BIS, the EEG segments with artifacts and suppressed EEG are identified and rejected, thereafter the index is calculated by combining the EEG features selected from a set of candidate bispectral and power spectral variables. While conventional spectrum analysis represents the power of frequency components of the EEG waveform, the bispectral analysis quantifies the inter-frequency

relationship. The bispectral index provides a measure of the effects of anaesthetics and other pharmacological agents on the hypnotic state of the brain. It was reported that the BIS both correlated well with the level of responsiveness and provided an excellent prediction of the loss of consciousness, and that BIS is linearly correlated with the blood concentration of propofol and the magnitude of the cerebral metabolic reduction caused by propofol and isoflurane anaesthesia (Doi et al., 1997; Leslie et al, 1995). This suggests that a physiologic link exists between the EEG and cerebral metabolism during anesthesia that is mathematically quantifiable. The bispectral index has been prospectively validated with a large clinical database (Doi et al., 1997; Leslie et al, 1995).

We have developed a closed-loop system in which raw EEG is collected from the patient, processed to produce the derivative Bispectral Index which is then fed to an anaesthesia control system which incorporates a Proportional Integral Derivative (PID) controller with additional rules which calculates an appropriate target drug concentration for the patient and adjusts the rate of infusion of the anaesthetic agent by controlling a clinical infusion pump. We have used published data on the distribution within the body and brain response to a commonly used anaesthetic agent, propofol, and simulated a large population of "virtual patients" (Leslie et al, 1995; Gepts et al, 1987). This has allowed us to evaluate how our closed-loop system might perform when deployed on a range of individual patients.

2. Methods

2.1 Pharmacokinetics and Pharmacodynamics

In modern medical practice, anaesthesia is usually induced by an intravenous injection of an anaesthetic agent (hypnotic). It may then be maintained by a continuous infusion of the same drug. The rise and fall in blood concentration of a commonly used anaesthetic agent, propofol, following a single dose is illustrated in Figure 1. The decline in blood anaesthetic concentration following a single dose may be described as some other series of exponentials (see Equation 1) (Egan, 1996).

$$D_p(t) = \sum_{i=1}^{n} A_i e^{-\lambda_i t}$$

$$Cp_{CALC}(t) = I(t) * D_p(t) \qquad (1)$$

Where $D_p(t)$ is the disposition function of the drug in the body after a bolus infusion, exponents λ_i are the inverse of the half-lives(half-life = $0.693/\lambda$), coefficients A_i are the relative contributions of each half-life to overall drug disposition, and the integer n is the number of exponentials. If the infusion rate over time is $I(t)$, then the plasma drug concentration over time is $Cp_{CALC}(t)$. The operator * denotes the convolution algorithm.

These equations may be used to describe the body in terms of a series of connecting compartments between which the drug (initially administered into the blood) equilibrates by a series of micro rate-constants

(Figure 2).

In medical anaesthetic practice, it is common experience that there is a delay between the administration of drug and the peak effect. This may be confirmed by electronic monitoring of the electroencephalogram (EEG). When blood concentration and brain effect are simultaneously measured, this latency of drug action may be clearly seen (Figure 3). When drug concentration and EEG measured brain effect are plotted against each other, a hysteresis loop is demonstrated (Figure 4) and the mathematical model of drug distribution may be extended to include an additional compartment known as the effect site which reflects the latency between peak blood concentration and drug action (Levy, 1998; Holford and Sheiner, 1981).

2.2 Target Controlled Infusion (TCI)

A clinical application of pharmacokinetic models such as Equation 1 has been developed by solving the equations necessary to calculate the changing quantities of drug which must be administered across time to achieve stable blood concentrations. The initial bolus injection and subsequent changes in infusion rate necessary to achieve and maintain a stable clinical concentration of the anaesthetic drug, propofol, are illustrated in Figure 5.

Simulations such as these have advanced our understanding of drug distribution and effect, however, they reflect the average response of a population of patients and do not accommodate inter-patient variability. Figure 6 illustrates the simulated response of 9 patients with slightly different pharmacokinetic characteristics to whom a standard scheme of drug infusion has been applied. We see that application of this standard infusion scheme results in different drug concentration/time profiles in each patient and this variability must be considered if we are to use an automatic system to induce and maintain clinical anaesthesia.

2.3 Closed-loop Anaesthesia

In a closed-loop anaesthesia system, an indication of the individual patient's "depth of anaesthesia" is derived from the electroencephalogram (EEG) and an EEG derivative such as the Bispectral Index (BIS) is fed to a central controller. The controller may control the drug infusion directly or, alternatively, use a process of pharmacokinetic (drug distribution) or pharmacodynamic (drug effect) modelling as described above to improve the system's control of drug infusion to the patient. We have implemented closed-loop intravenous anaesthesia using a standard control theory with a proportional integral derivative (PID) controller which quantifies the error between the measured Bispectral Index and a pre-set target. This, with the addition of some additional rules, is used to adjust the target concentration of drug to the individual patient to which is then implemented using a modified target controlled drug infusion system.

2.4 Design Consideration and Constraints:

The control system was designed and optimized based upon the published pharmacokinetic/dynamic data which were obtained from a certain range of patients (Gepts et al., 1987; Vuyk et al, 1995), outside this population it would result in a larger induction overshoot or a longer time to achieve stable level of anaesthesia. The basic assumption of the control system is that the pharmacokinetics and pharmacodynamics are linear.

2.4.1 Choice of control strategy

A control strategy combining a PID controller with a reference model is used in the simulation. Usually, PID control is effective for a process containing some unknown dynamics like the one under investigation, and can give satisfactory results. The reference model provides a general guide for the PID control, especially for the size of the induction bolus. The use of a reference model will reduce the risk of a large and sudden increase in infusion rate (this will be spread over a period of time if the physical limit on maximum infusion rate applies) as the adjustment from the PID controller is only an offset to the guess from the reference model, and the adjustment is therefore small and safe to the patients. If the feedback signal is absent or other emergent events occurred, the reference model can automatically take over the control to force the system to run in TCI mode until everything returns to the normal status. Finally, referring to the literature this control strategy has not been investigated.

2.4.2 Validation of the underlying model

The PID controller has achieved huge success in industrial process control and the reference model has also been successfully used in TCI (Glen, 1998). The use of the reference model will provide safer control on drug infusion while PID controller gives the infusion system ability to dynamically respond to the real time measurement of anaesthetic depth of patients.

3. Simulation

Before implementing closed-loop anaesthesia in practice, we simulated the individual components of our proposed system and tested its response to a population of "virtual" patients with different pharmacokinetic and pharmacodynamic

characteristics. Figure 7 illustrates the sequential changes in the Bispectral Index that might be programmed for a particular patient and illustrates how our population of virtual patients might respond when anaesthetised.

4. Clinical Testing of Closed-loop Anaesthesia

We have subsequently used our closed-loop system to anaesthetise human volunteers and this is illustrated in Figure 8.

5. Conclusion

Mathematical modelling of blood concentrations and EEG derivatives after drug administration to human permit the elaboration of mathematical models. Implementation of these models has allowed the clinical development of Target Controlled Anaesthesia which is now commercially available. We have developed this technique further by using standard industrial control theory to adjust drug administration in response to an EEG derivative, the Bispectral Index measured from each individual patient. Because the characteristics of individual patients are variable, we simulated the response of our system to a wide range of individual patients prior to successful testing of the closed-loop system in human.

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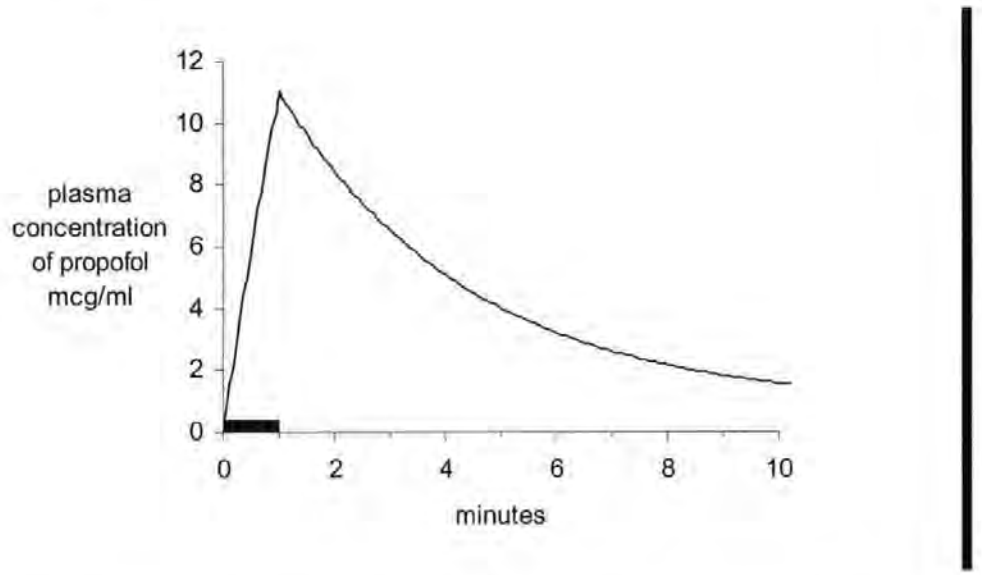
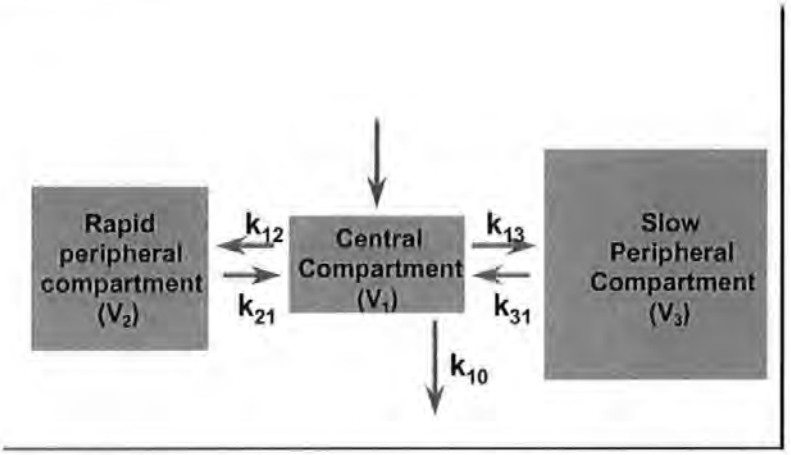
Legends for Figures

Figure 1



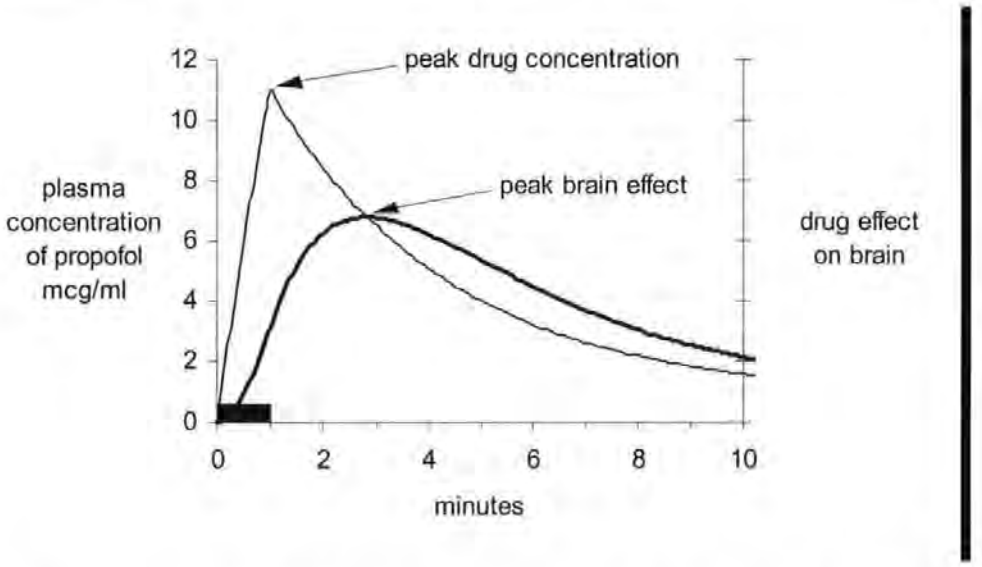
Changes in plasma concentration of an intravenous anaesthetic drug, propofol which is infused for a period of one minute (black bar). Note that the concentration of the drug rapidly reaches a peak and then gradually decays in a poly-exponential manner.

Figure 2



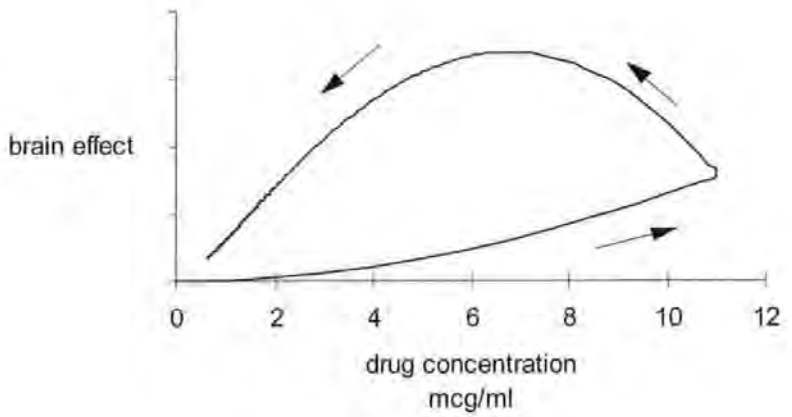
A three compartment mathematical model describing the distribution and elimination of the anaesthetic drug, propofol. The drug is administered to a central compartment V_1 which equilibrates with two other compartments V_2 and V_3. The transfer of drug between compartments is described by micro rate-constants k_{12} etc. The drug is eliminated from the central compartment at a rate determined by k_{10}.

Figure 3



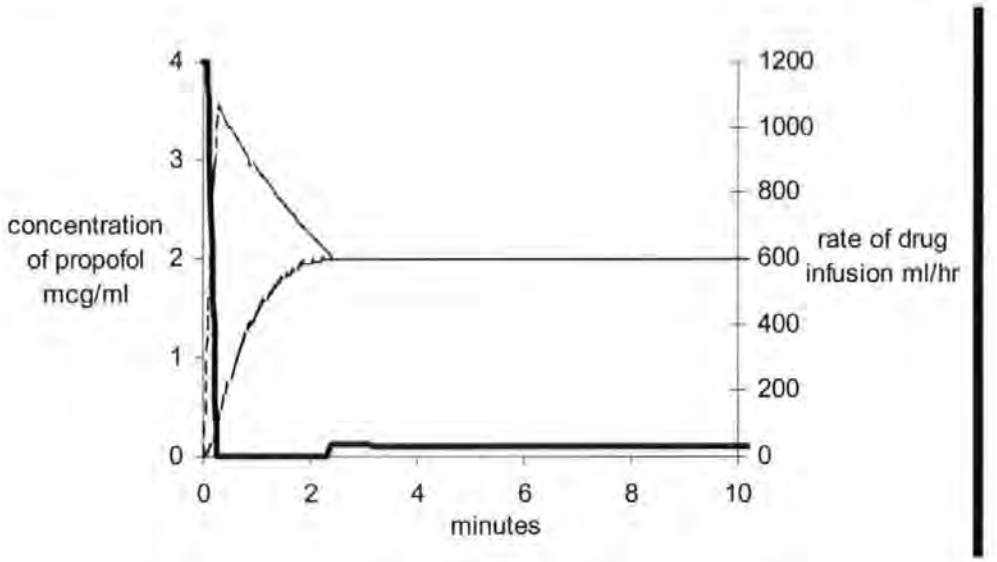
Following a single dose of the human anaesthetic agent, propofol, there is a delay between peak concentration of the drug in the blood and the peak effect on the brain. Blood concentration of the intravenous anaesthetic agent, propofol, following a single dose is illustrated by the thin line. An electroencephalogram (EEG) derived measured brain effect is indicated by the heavy line. Note the delay between the two peaks.

Figure 4



The plasma concentration and brain effect data from Figure 3 can be plotted against each other to form a hysteresis loop. The passage of time is indicated by arrows. Note that concentration initially arises rapidly and well in advance of the onset of drug action.

Figure 5



Implementation of a complex infusion scheme designed to achieve a stable drug effect in man. In order to achieve the desired drug effect (lower thin line), the rate of drug infusion is changed every few seconds (thick line). Note that the rate of drug infusion is initially very rapid i.e. a bolus of the drug is given, the pump then switches off and re-starts 2 minutes later at a much lower rate. This infusion scheme gives a high initial concentration of drug in the plasma (upper thin line) which produces an increasing brain effect (lower thin line). A stable brain effect is achieved within 2.5 minutes.

Figure 6

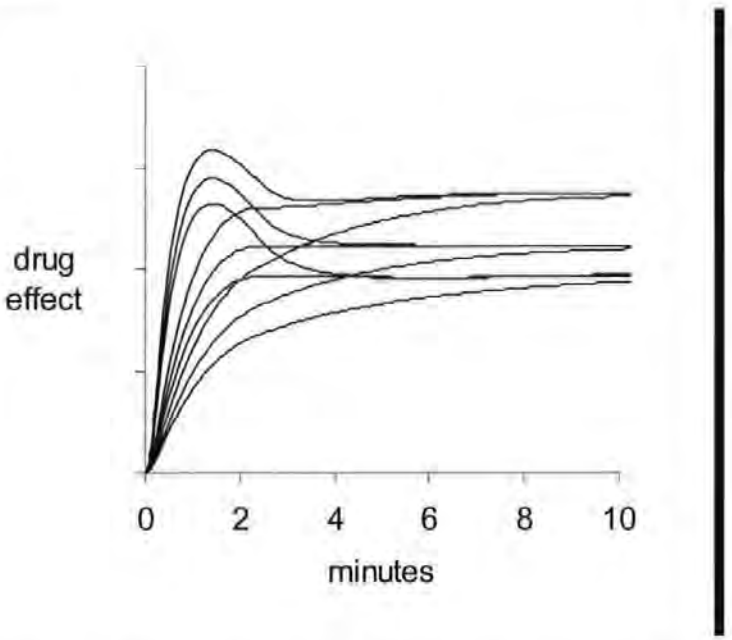
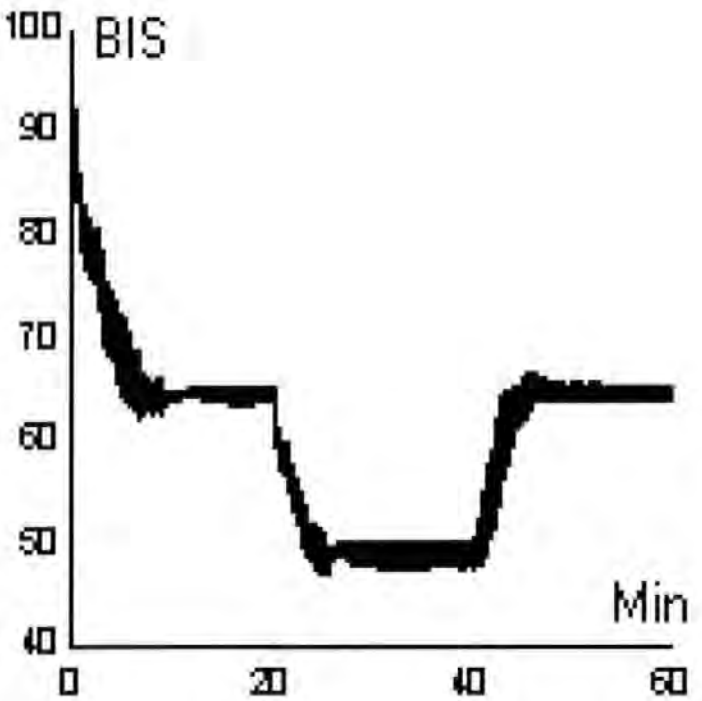


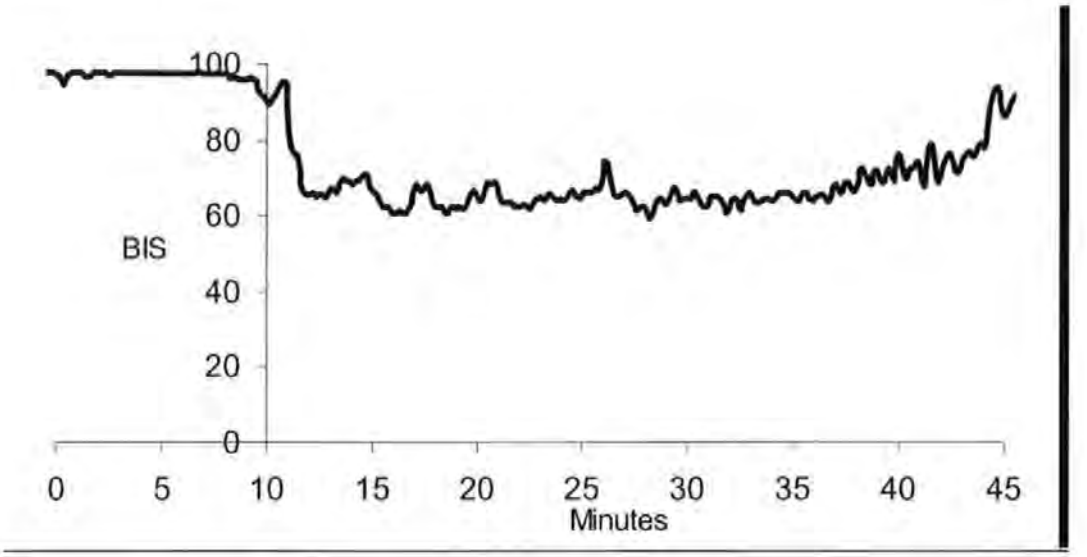
Illustration of inter-patient variability. The infusion scheme developed in Figure 5 has been implemented in 9 virtual patients with different pharmacokinetic characteristics. Notice that the same infusion scheme produces differing drug effect/time profiles in individual patients.

Figure 7



The traces are the simulated response of 3125 individual virtual patients anaesthetised by a closed loop anaesthesia system. The system is set to depress the Bispectral Index (BIS), a measure of consciousness from a baseline (conscious) level of 100 to a lightly anaesthetised level of 65 from 0-20 minutes, to a deeper level of 50 between 20 and 40 minutes, back to 65 between 40 and 60 minutes when anaesthesia is discontinued and the virtual patient allowed to recover. Note that there is some initial instability however the responses of the virtual patients are tightly grouped suggesting that if the system has been correctly modelled there is a low risk of excessive responses or gross instability in man.

Figure 8



Anaesthesia of a single human volunteer using a bispectral index (BIS) derivative of the electroencephalogram (EEG) and a Proportional Integral Derivative (PID) controller with additional rules. The system has successfully induced and maintained light anaesthesia between the 10^{th} and 45^{th} minutes with a target Bispectral Index (BIS) of 65.