FEEDBACK CONTROL OF SEDATION AND GENERAL ANAESTHESIA

Anthony Absalom, MBChB, FRCA, ILTM

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Contents

Appendices

Declaration

I, Anthony Ray Absalom, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise), and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Date

Abstract: Feedback control of sedation and general anaesthesia

The man aim of my studies was to investigate the safety and efficacy of two modes of feedback control of sedation and anaesthesia. A secondary aim was to add to the body of knowledge on the Bispectral Index (BIS). I also wrote a computer program (BISCLAN) that was used in all the studies as a BIS data management tool, and in some studies for manual or automatic control of a propofol infusion.

Two studies did not involve feedback control, but were performed to further our understanding of the BIS. For one, I recorded BIS values and the times at which clinical events occurred during 200 general anaesthetics, and studied memory of perioperative events. Broad variation in BIS values at similar levels of anaesthetic depth was found, although there was good separation between the majority of BIS values found during periods of consciousness and unconsciousness. BIS values on awakening were not predictive of memory for subsequent events. For the second study I investigated the effects of the stimuli used to generate auditory evoked potentials on consciousness levels and the BIS, during sedation and anaesthesia. No effect was found.

Three studies of BIS-guided computer control of anaesthesia and sedation were performed. Control performance was assessed in terms of clinical adequacy of anaesthesia and with recognised mathematical criteria. BISCLAN was able to control anaesthesia successfully. Cardiovascular parameters were stable in all patients. With two exceptions, operating conditions were also adequate. Control parameters during sedation and anaesthesia were acceptable and compare favourably with those found in other studies. Two studies of a second mode of feedback control of sedation (patient-maintained sedation) were performed. In both the goal was to determine if system safety was sufficient to prevent volunteers from purposefully inducing loss of consciousness. Sedation scores, propofol concentrations and physiological data were recorded. Secondary data included BIS values, and tests of memory for words. In one study a revised version of a previously developed blood concentration targeted infusion system was used, and in the other an effect-site targeted system. One subject in the second study became over-sedated, but no subjects lost consciousness. There was correlation among BIS values and propofol concentrations, and among BIS and propofol concentrations and the likelihood of memory for words. Several subjects remained conscious during periods when the BIS was < 60.

Anthony Ray Absalom, April 2004

Contributions to projects relevant to this thesis

Project 1:

Development of a BIS data management and closed loop control system (Chapter 9)

I planned and wrote this computer program myself. The serial port communication unit was purchased as freeware from Mr. R Crowther, and the control algorithm was adapted from one used in an AEP system developed in Glasgow.

Project 2:

Correlation between BIS and clinical end-points (Chapter 11)

The idea was mine, I wrote the protocol and ethics committee application, planned and executed the project, and analysed the data.

Project 3:

Effects of the clicks of an AEP stimulus on the BIS (Chapter 12)

The idea was mine, I wrote the protocol and ethics committee application, planned and executed the project, and analysed the data.

Project 4:

Closed-loop control of propofol anaesthesia during combined regional and general anaesthesia (Chapter 13)

The idea was mine, I wrote the protocol and ethics committee application, and planned and executed the project. Dr Nick Sutcliffe inserted the epidural catheters and was the consultant responsible for the clinical care of the patients.

Project 5:

Closed-loop control of propofol anaesthesia during propofol/remifentanil general anaesthesia (Chapter 14)

The idea was mine, I wrote the protocol and ethics committee application, and I planned and executed the project. Professor Gavin Kenny assisted with the protocol and ethics application.

Project 6:

Safety of patient-controlled sedation using a revised blood-targeted TCI (Chapter 17)

Dr. Fiona Henderson wrote the protocol and the ethics committee application. I assisted her with some aspects of the protocol, and with the data collection. I analysed the data.

Project 7:

Safety of patient-controlled sedation using an effect-site targeted TCI (Chapter 18)

Dr Sutcliffe and I developed the idea and the protocol. I wrote the ethics committee application, planned and executed the study, and analysed the data. Dr. Frank Engbers wrote the software for the effect-site targeted propofol infusion system.

Project 8:

Computer control of sedation using the BIS (Chapter 19)

The idea for this study was mine. Dr. Kate Leslie and I wrote the protocol and the ethics committee application. I assisted her with the planning and execution of the study and with the data analysis.

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I would also like to thank Aspect Medical Systems International who loaned me the BIS monitors and donated the electrodes used in my studies. Finally, for their patience and assistance, my thanks go to the staff in the operating theatres where the studies were performed.

Dedication

This thesis is dedicated to my wife Cathy, and my children Alice, Jasmine, and Louis

Introduction

Aims of this thesis

In comparison with some of the branches of medical practise, anaesthesia is a recent development, dating back to the 1840's. Since then rapid and substantial developments have occurred despite the fact that our understanding of many aspects of anaesthesia remains limited.

Initially, anaesthesia could only be administered via the inhalational route. The discovery of means of administering drugs via the intravenous route, combined with the development of neuromuscular blocking drugs and intravenous anaesthetic agents suitable for induction and maintenance of anaesthesia, has heralded a new age in surgery and anaesthesia. Among many other benefits, these discoveries have made possible a huge range of operative procedures, and have enabled smooth, rapid and pleasant induction and emergence from anaesthesia. However, these discoveries have also conspired to introduce the risk, in paralysed patients, of inadvertent conscious awareness during periods of inadequate anaesthesia. Awareness during anaesthesia has serious consequences for all concerned and remains a feared complication of anaesthesia. Despite the efforts of numerous investigators around the world, the goals of developing a gold standard method of measuring anaesthetic depth and a fail-safe method of preventing awareness have not yet been achieved.

The aim of my studies, and this thesis, was to add to the body of knowledge on monitoring of sedation and anaesthesia, and to apply new technologies to improve control of sedation and anaesthesia.

Chapter 2

Historical background

Humphrey Davy discovered the analgesic properties of nitrous oxide in 1800, calling it "laughing gas," and in 1844 Horace Wells manufactured and used the gas for painless extraction of teeth. [1] Unfortunately, instead of fame, Wells achieved notoriety, after a public demonstration of the use of nitrous oxide in January 1845 was deemed a failure when the patient cried out in pain during the operation.[1] Crawford Long successfully administered ether for the excision of a tumour from the neck of James Venable in 1842, but failed to report this.[2] Thus, WTG Morton is regarded as the father of anaesthesia, as he gave the first successful public demonstration of anaesthesia when he used ether at the Massachusetts General Hospital, on 16th October 1846, to enable the "painless" excision of a tumour from the jaw of Gilbert Abbott.

For many decades thereafter the inhalation continued to be used for induction and maintenance of anaesthesia. The early methods of administration of anaesthesia seem crude – the apparatus was simple, and the available anaesthetic agents had many adverse effects, several of which were serious. Because the agents were highly soluble in blood, induction of anaesthesia was slow, and recovery times were very long. There was also no method of measuring or controlling the inspired or expired concentration.

Nonetheless, as the early methods depended on spontaneous respiration by the patient (there was no method of mechanical ventilation of the lungs) there was an inherent safety mechanism – the patient's pharmacodynamic responses to the drug acted as a feedback control system. For example, if the airway became obstructed during induction of anaesthesia, the delivery of anaesthetic agent to the lungs ceased, so that the depth of anaesthesia decreased and the airway reflexes returned. Likewise, during maintenance of anaesthesia, if the patient became too deeply anaesthetised, respiration

was depressed, so that the rate of delivery of drug to the lungs decreased, causing a decrease in the depth of anaesthesia. Conversely, if the patient was inadequately anaesthetised, the respiratory rate increased, and the rate of drug delivery increased.

With the introduction of methods of mechanical ventilation and intravenous administration of drugs, and the discovery and use of intravenous anaesthetic agents and muscle relaxants, these safety mechanisms were circumvented.

Intravenous administration of drugs

Sigmund injected opium intravenously in 1665, Rynd used a trochar and cannula for injection of morphine in 1845, and Pirogoff used intravenous ether in animals in 1847. These early attempts involved the use of custom-made equipment in an era when the value of sterilisation of equipment was only beginning to be recognised. Other than these early pioneering attempts drugs were rarely administered intravenously until the invention of the hypodermic syringe and needle by Alexander Wood of Edinburgh in 1853.

The ability to inject drugs into the vascular space paved the way for the use of muscle relaxants and intravenous anaesthetic agents. These developments made it possible to bypass the patient's inherent safety system - the ability to control, to a degree, the dose of anaesthetic administered - so that muscle relaxation and the depth of anaesthesia no longer depended on the patency of the airway, and the patient's respiratory drive. After intravenous induction of anaesthesia, and paralysis by a neuromuscular blocking drug, the patient depended on the clinical skill of the anaesthetist to maintain a patent airway, and to control the depth of anaesthesia to a level sufficient to avoid awareness, or overdose and toxicity.

Mechanical ventilation, intubation of the lungs

Vesalius described tracheal insufflation in animals in 1555, and tracheal intubation was used by several early anaesthetists, usually for prevention of aspiration pneumonia, or for relief of airway obstruction. Pioneers included Snow, who performed tracheostomies on animals in 1858, and MacEwen, of Glasgow, who performed oro-tracheal intubation in humans in 1878.

Artificial ventilation of the lungs has a more recent history. Although experiments involving artificial ventilation of animals were described in the early 1800's, and Janeway described an early ventilator in 1913, artificial ventilation in humans was only introduced into clinical practise in 1934, by Guedel and Treweek. By assisting respiration with a bag, they were able to hyperventilate the lungs with ether, producing hypocapnia, deep anaesthesia and apnoea. Thus even before the use of muscle relaxants, anaesthetists were able to break the link between respiratory drive and dose of anaesthetic agent delivered.

Muscle relaxants

The introduction of muscle relaxants into clinical practise has been the most important factor contributing to the problem of intraoperative awareness. Curare was shown, by Bernard in 1850, to act as an antagonist at the neuromuscular junction, and was used shortly thereafter for the treatment of tetanus. In 1939 it was used to attenuate the convulsions during metrozol-induced convulsive therapy. Griffith and Johnson were the first to use suxamethonium for muscle relaxation during anaesthesia (in 1942). Since then numerous other drugs have been discovered and developed. They are all antagonists at the neuro-muscular junction, and none of them have hypnotic properties. Suxamethonium, a depolarising neuromuscular blocking agent is short-acting, although in patients with deficient or absent plasma pseudocholinesterase enzymes, prolonged

paralysis is possible. The non-depolarising neuromuscular blocking agents are medium- or long-acting.

The introduction of muscle relaxants made it imperative for anaesthetists to be able to maintain and control the airway during anaesthesia. They also made it more important for the anaesthetist to be able to assess the depth of anaesthesia. Clinical signs of anaesthesia were of use in this regard, and will be discussed in a subsequent chapter of measurement of depth of anaesthesia.

Monitoring of inhalational anaesthetic agent concentrations

Although there is a correlation between the end-tidal concentration and the arterial partial pressure of a volatile anaesthetic agent, the correlation is weakened by increasing amounts of ventilation/perfusion mismatch. A study performed by Frei found that the end-tidal isoflurane concentration overestimated the arterial partial pressure by an average of 20%. [3]

Eger developed the concept of MAC (minimum alveolar concentration) in 1965.[4] MAC is a measure of potency of volatile anaesthetic agents, and is defined as the steady-state end-tidal concentration of anaesthetic agent required to prevent 50% of patients from moving in response to a standard surgical stimulus. MAC values have been calculated for all inhalational anaesthetic agents. Real-time monitoring of the concentration of anaesthetic agents in anaesthetic breathing systems has become routine in recent decades. With continuous measurement of the end-tidal anaesthetic concentration, and knowledge of the MAC for the agent in use, the anaesthetist has a rough (statistical) guide to the adequacy of the anaesthetic dose being delivered.

MAC has other limitations. When patient movement is undesirable, administration of one MAC of anaesthetic agent (as the sole anaesthetic agent) is likely to result in inadequate anaesthesia in 50% of patients. Secondly, MAC is age related - it

decreases by 6% per decade of life [5] - and is influenced by co-administered drugs such as nitrous oxide (MAC of nitrous oxide is 105%), opiates [6,7] and benzodiazepines.[8;9] Thus it is difficult to extrapolate between MAC for an agent (which applies to a population, not an individual) and the anaesthetic requirements of an individual patient. Because of this many anaesthetists err on the side of caution, and administer more anaesthetic agent than is required.

Finally, recent developments have cast doubt over the validity of movement in response to surgical stimulation as a sign of inadequate anaesthesia. Anaesthesia is a dynamic balance between drug-induced hypnosis and analgesia, and the level of surgical stimulation. Absence of movement is a surgical requirement. Patient movement does not necessarily represent awareness, or even the presence of a functioning forebrain, as the movement response to painful stimuli in unconscious patients is entirely mediated at the spinal cord level. [10;11] Despite these limitations, end-tidal anaesthetic agent monitoring remains a useful tool during inhalational induction or maintenance of anaesthesia. It confirms that the volatile agent is being delivered, and indicates the measured concentration of anaesthetic agent in the breathing system, which in turn gives an approximation of the arterial concentration.

Intravenous anaesthetic agents

The pioneer of intravenous anaesthesia is Pierre-Cyprien Ore, who described the intravenous administration of chloral hydrate to 36 patients in1875.[12] Forty years later Federov used intravenous hedonal, and Burckhardt chloroform and ether. Nonetheless it was only after the discovery of shorter-acting barbiturates that this route of administration of drugs for anaesthesia became commonplace.

Somnifaine (Aprobarbitone) was the first barbiturate to be used for induction of anaesthesia (Bardet, 1924). Intravenous induction of anaesthesia became popular after Helmut Weese used hexobarbitone in 1932. Thiopentone was introduced into clinical practice in 1934. Methohexitone and thiopentone are still in use today. When a single dose of either is used for induction of anaesthesia, the duration of effect is only a few minutes. Nonetheless they are not suitable for maintenance of anaesthesia, because they tend to accumulate when administered by infusion, leading to a prolonged recovery phase.

Etomidate, first used in man in 1973, has pharmacokinetic properties that make it suitable for use by continuous infusion for sedation or maintenance of anaesthesia, and helped lead to a resurgence in interest in the use of intravenous anaesthesia. Unfortunately, its use is limited by the problem of adrenal suppression. Single doses and infusions in healthy patients are associated with short-term, reversible suppression of cortisol formation.[13-16] In critically ill patients, prolonged infusions are associated with multiple organ failure and death.[17] In these patients I have shown that even single doses interfere with adrenal function for more than 24 hr.[18] Etomidate is thus usually only used for single bolus induction of anaesthesia, where there are significant reasons for avoiding alternative agents. Althesin was another agent that showed great promise, but it was solubilised in Cremophor EL, and was withdrawn from use because of a high incidence of allergic reactions.

Propofol was first introduced in the mid-1980's. It has a pharmacokinetic profile suitable for use by infusion for induction and maintenance of anaesthesia, and for sedation. [19;20] Pain on injection occurs in less than 50% of patients, but otherwise propofol is associated with a pleasant and smooth induction of anaesthesia. Recovery is rapid and clearheaded, and is associated with a lower incidence of post-operative nausea

and vomiting than when thiopentone and the inhalational anaesthetic agents are used.[21;22] Some studies have shown that propofol possesses anti-emetic effects.[23]

The growth in popularity in intravenous anaesthesia may also be attributed to environmental concerns associated with inhalational agents. Volatile anaesthetic agents and nitrous oxide are associated with local and global pollution, damage to the ozone layer, and a contribution to the greenhouse effect; and there are concerns of teratogenesis, interference with DNA synthesis and spontaneous abortion associated with nitrous oxide. [24;25] A recent study comparing neutrophil apoptosis in anaesthetists chronically exposed to volatile anaesthetic agents suggested that this exposure causes damage equivalent to smoking 15 cigarettes per day.[26]

The availability of a drug suitable for use by infusion, advances in the knowledge of pharmacokinetics, and the availability of powerful microprocessors have enabled the introduction of target-controlled infusion systems. These infusion systems are controlled by microprocessors (programmed with pharmacokinetic parameters) that enable the user to select the desired blood concentration of the drug. When the "target" concentration is increased the system administers a rapid infusion to produce an almost step-wise increase in the blood concentration. After achieving the target the system delivers an infusion to maintain that concentration, taking into account distribution of the drug into different tissues/compartments and drug metabolism. When the target is reduced, the system stops infusing the drug until the blood concentration has reached the new target, thereby achieving as rapid a reduction in concentration as possible. Propofol is the only drug for which there are commercially available TCI systems. Several companies now make TCI systems for propofol – all incorporate a "Diprifusor" microprocessor (AstraZeneca, Macclesfield, England). [27] These systems are in use in more than 100 countries.

The advent of intravenous anaesthesia was an important milestone in the history of anaesthesia. As mentioned previously, inhalational anaesthesia in a spontaneously breathing patient is somewhat self-limiting. Once injected, a drug cannot be retrieved. Thus the availability of intravenous anaesthetics and of neuromuscular blocking drugs has made it all the more important for anaesthetists to be able to judge the dose of anaesthetic drug required, and to be able to assess the depth of anaesthesia.

Dose requirements of intravenous agents for induction and maintenance of anaesthesia

During induction of anaesthesia anaesthetists usually titrate the dose according to clinical effect. After a bolus injection of a drug there is a delay before a clinical effect is seen, as time is required for the drug to reach the brain, and then diffuse into and interact with the site of action. If the anaesthetist gives a subsequent dose without allowing for this delay, the patient may receive an excessive dose. The ED50 (effective dose required to prevent a specified response in 50% of patients) is a measure of potency for intravenous anaesthetic agents, analogous to the MAC for inhalational agents. Nonetheless, it provides a useful guide to the choice of initial induction dose when a bolus dose is to be used for induction, and has been determined for different drugs. These doses are usually calculated per kg of total body mass.[28] Some authors advocate the use of lean body mass.[29] As always the final dose used should be titrated to clinical effect.

The concept of MAC for inhalational agents was extended to intravenous anaesthesia by Sear and Prys-Roberts, who introduced the concept of minimum infusion rate (MIR).[30;31] This method attempted to quantify the relationship between infusion rate and effect, but has limited usefulness because, before steady state blood and brain

concentrations are achieved, the relationship between infusion rate and concentration is not constant.

When infusions are used for induction and maintenance of anaesthesia the EC_{50} (effective concentration required to prevent a response to a specified stimulus in 50% of patients) is a useful concept.[32] This is sometimes referred to as the Cp50 (plasma concentration of a drug required to prevent a response in 50% of patients). The ED50 and EC50 are influenced by age, population group, gender [33] and co-administration of adjuvant drugs (Table 2.1). As with ED50, the EC50 and EC95 have been investigated using a variety of endpoints and clinical situations. Other endpoints that have been studied include loss of eyelash reflex, loss of response to verbal command and tactile stimuli,[34] and haemodynamic reponses to intubation, skin incision, opening of peritoneum, and intra-abdominal surgery.[35] It must of course always be remembered that the site of action of most anaesthetic drugs is not in the vascular compartment. After a change in infusion rate there is a delay before equilibration between the blood and effect-site concentrations occurs. EC values refer to blood concentrations, but these are only relevant after equilibration has been reached.

Modern computers of even moderate processing power are easily able to estimate the blood and brain (or "effect-site") concentration generated by any infusion regimen of an intravenous anaesthetic drug, based upon population pharmacokinetic/pharmacodynamic (PK/PD) models. Commercially available TCI devices such as the Diprifusor display the predicted concentrations, and computerised pharmacokinetic simulator programs (such as the TIVA Trainer [F Engbers, Leiden, Netherlands]) can calculate the EC50 of propofol in the presence different blood opioid concentrations (extrapolated from data from a specific female population receiving alfentanil for abdominal surgery[35]).

Of course all these predicted concentrations may be completely irrelevant if the drug is not actually entering the patient's blood circulation (as would occur if the drug administration set became disconnected or the intravenous cannula dislodged or migrated into the perivascular tissues). At present there is no real-time direct monitor of the concentration of the intravenous anaesthetic agents in the blood. Even if a monitor is developed, it will have limited clinical usefulness for two main reasons. Firstly the dose of hypnotic required changes with time in an individual patient according to the intensity of surgical stimulus, and secondly the dose required to prevent a response to a given stimulus varies widely between patients because of inter-individual pharmacodynamic and pharmacokinetics differences. A real-time monitor of anaesthetic effect is thus particularly desirable during intravenous anaesthesia.

Awareness

Awareness during surgery is as old a problem as the history of anaesthesia. As mentioned earlier the public demonstration of nitrous oxide, by Wells, in 1845 was deemed a failure because the patient cried out on incision. The first demonstration of ether anaesthesia, by Morton 1846, was deemed to be a success even though the patient was afterwards able to recall the operation.[36] In those early days, awareness was usually obvious to those present, because the patient was able to move and speak if aware. Inadvertent awareness is a serious problem during the modern era because it is not always obvious in paralysed patients.

Conclusion

This chapter has summarised some of the advances in anaesthesia in the past 150 years, highlighting those that, when employed in clinical practise, override the patient's

protective feedback mechanisms, giving rise to some of the risks still present in modern anaesthetic practise. After intravenous induction of anaesthesia, and muscle relaxation, failure to obtain a patent airway and failure to intubate the trachea remain serious risks. Likewise during maintenance of anaesthesia, administration of an inadequate dose of anaesthetic agent can occur causing inadvertent awareness, whereas an overdose can cause adverse cardiovascular and respiratory effects. Thus, measures of anaesthetic effect are required to help anaesthetists to judge the dose required for optimal anaesthetic depth. Before being able to measure anaesthetic depth it is first necessary to understand what anaesthesia is, and so the following chapter deals with the concepts of anaesthesia and awareness.

Table 2.1

Summary of studies that have calculated the concentration of propofol required to prevent a response to painful stimuli in 50% of patients.

Adjuvant drugs	**EC50 (μg/ml)**	**Reference**
Propofol alone	14.3	[37]
Propofol alone	15.2	[38]
Propofol alone	6.8 †	[39]
N_2O 60%	1.7 *	[40]
N_2O 67%	4.9 †	[39]
Temazepam premedication	8.1	[41]
Temazepam premedication, N_2O 60%	5.4	[41]
N_2O 60%, morphine, esmolol	2.85	[42]
Fentanyl 3 ng/ml	1.67	[38]

* Electrical stimulation

† These values were predicted values calculated using the Marsh kinetic model.[43] All other concentrations values in the table were measured.

Chapter 3

Anaesthesia and awareness

In the previous chapter I highlighted how developments in intravenous anaesthesia and muscle relaxation have increased the risks of undetected awareness during inadequate anaesthesia, increasing the need for methods of accurate assessment and control of depth of anaesthesia. In this chapter anaesthesia and awareness will be defined and discussed, while in chapter 4 some of the methods of measuring depth of sedation and anaesthesia will be discussed.

WHAT IS ANAESTHESIA?

The Greek philosopher Dioscorides was the first person to use the term "anaesthesia," when describing the narcotic effects of the plant *mandragora* in the 1st century AD. The word again appeared in the 1771 edition of *Encyclopaedia Britannica* where it was defined as a "privation of the senses". Plomley was the first, in 1847, to define depth of anaesthesia. He described three stages of anaesthesia: intoxication, excitement and deeper narcosis. Soon afterwards Snow described "five stages of narcotism."[44;45] In 1937 Guedel published a classification of the clinical signs of ether anaesthesia, defining four stages representing increasing depth of anaesthesia, with the third stage sub-divided into 4 planes of increasing depth.[46]

The nature, and physiological and pharmacological mechanisms of the state of anaesthesia are poorly understood, making it difficult to define the state of anaesthesia. Patients are often told that they will be "asleep" but of course, contrary to the state of sleep, they will usually not wake up when subjected to painful stimuli. Our lack of understanding of the state of anaesthesia is so fundamental that there is no consensus on

whether anaesthesia is a binary or a continuous phenomenon. Some anaesthetists believe that anaesthesia is a binary phenomenon and that there is no such thing as "depth of anaesthesia" - anaesthesia is either present or absent – whereas others (probably in the majority) believe that anaesthesia is a continuum. [47]

So, when is anaesthesia present? As anaesthesia is difficult to define, it follows that it is difficult to say when anaesthesia is present, and generally it is easier to define phenomena that are absent during adequate anaesthesia. Different people have different requirements of the anaesthetic state, and so will define anaesthesia according to the presence or absence of their requirements. The surgeon, for example, may define anaesthesia as a state in which the patient does not move when subjected to a surgical stimulus. Patients are more concerned about amnesia and lack of awareness. Anaesthetists should be concerned about all the above as well as haemodynamic stability.

Anaesthesia has been described as a triad of "hypnosis, muscle relaxation and analgesia".[48] Although this definition is still commonly used, these are separate phenomena, do not necessarily co-exist, and may arise as separate pharmacological actions of one or more drugs.[49] The muscle relaxants, for example, only have an effect on muscle power and thus the presence of muscle relaxation does not imply the presence of hypnosis. Inhalational anaesthetic agents give rise to hypnosis and some muscle relaxation, but lack analgesic effects. In recent decades it has been shown that in unconscious patients hypnotic drugs prevent movement in response to painful stimulation by an action at the spinal cord whereas, prevention of consciousness and recall are mediated via actions at the cerebral cortex.[11] Movement following painful stimulation may occur thus in the presence of EEG burst suppression (indicating deep

levels of anaesthesia or profound neurologic dysfunction secondary to cerebral ischaemia), [11;50] or even in the presence of brainstem death.

Studies of awareness have shown that during periods of inadvertent intraoperative awareness patients do not always show the signs of sympathetic activation (such as tachycardia and hypertension) that anaesthetists are taught to expect.[51;52] Interestingly, it has also been shown that non-paralysed patients do not necessarily move during periods of inadvertent intraoperative awareness. [51]

Thus while lack of patient movement and prevention of haemodynamic responses may be necessary for surgery and for patient safety, the essential requirements for anaesthesia are hypnosis and amnesia. In keeping with this, Prys-Roberts has described anaesthesia as "a state in which, as a result of drug-induced unconsciousness, the patient neither perceives nor recalls noxious stimulation".[47]

Most anaesthetists now accept that depth of anaesthesia is a balance between hypnosis, analgesia and stimulation. Increasing concentrations of anaesthetic agents will give rise to a series of threshold events such as amnesia, loss of eyelash reflex, loss of response to command, and loss of movement and haemodynamic responses to increasingly painful stimuli. For given concentrations of anaesthetic and analgesic drugs, an increase in the severity of stimulus may be associated with return of some or all of these responses.

AWARENESS

Awareness can be defined as a state of unintentional return of consciousness during presumed general anaesthesia. During the return of consciousness there is a gradual return in cognitive processing – implying a degree of return of perception and memory formation.

Categories and consequences of awareness

Jones has described four categories of awareness during general anaesthesia (summarised in Table 3.1).[53] These categories are somewhat artificial, because they probably do not represent distrinct neurophysiological states. It is more likely that there is a continuum ranging from complete lack of awareness (with no implicit learning) through to the completely awake state. Nonetheless for the sake of standardisation and ease of communication is it useful to divide this spectrum into categories.

The first category has the most significant consequences. In this category the patient experiences an episode of intraoperative awareness, and later spontaneously recalls intraoperative events. Spontaneous recall does not necessarily manifest during the first 24 to 48 postoperative hours and may appear later.[51] Patients who experience this category of awareness are at risk of developing serious long-term psychological consequences such as depression, personality changes, and sleep disturbances including recurring dreams, nightmares and insomnia.[54] This is particularly the case if consciousness returns during periods of noxious stimuli in paralysed patients. In a prospective study of >10,000 patients undergoing general anaesthesia, Sandin identified 14 who experienced awareness whilst paralysed.[51] All 14 developed serious psychological consequences, such that in lectures Sandin describes these 14 as "emotional cripples" who are unable to function socially and occupationally. This category of awareness thus has severe consequences not only for the patients and their families but also for the health and social services of the state in which they live. In the same study Sandin identified 4 patients who were aware but not paralysed. These patients were far less traumatised by the experience, presumably either because they were not subjected to noxious stimuli while aware, or because adequate analgesia had been administered.

The second category of awareness, also referred to as "conscious perception," involves an episode of consciousness during which a patient responds to commands (e.g. opens eyes, or squeezes a hand), but later has no recall of these or other intraoperative events. The third category of awareness occurs when the patient does not exhibit consciousness during the intraoperative period and has no spontaneous recall of intraoperative events, but does later show evidence of implicit recall or learning. This evidence - elicited by techniques more commonly employed by psychologists – usually involves the playing of recordings of lists of words or a story to the patient via headphones, and later seeking a change in behaviour. Studies of learning under anaesthesia seem to suggest that learning is possible during conditions that would normally be regarded as constituting adequate anaesthesia.[55;56] Finally, for completeness the fourth category of awareness is "No awareness," and this is the result that should probably be the goal of every general anaesthetic.

The significance of Jones' second category of awareness is controversial. My personal opinion is that conscious perception represents an inadequate anaesthetic state, even if there is no later recall. Although there is no evidence at present to suggest that patients who experience awareness without recall may suffer adverse consequences, it is difficult to believe that "anguish unremembered" cannot be psychologically harmful.

Incidence of awareness

During the recent few decades many studies of the incidence of awareness have been performed (Table 3.2). Early studies showed remarkably high incidences. The reported incidence has since fallen with the latest large prospective study (performed in Sweden by Sandin) showing an incidence of verified cases of explicit recall among patients undergoing general anaesthesia of 0.18%.[51] More recently Myles and colleagues in

Australia performed a randomised blinded trial of the effect of Bispectral Index (BIS) monitoring on the incidence of awareness among cardiac patients undergoing general anaesthesia. They studied cardiac patients with poor left ventricular function (who were thus unable to withstand high doses of anaesthetic agents and were at high risk of awareness), and found an incidence of 0.16% among monitored patients compared with an incidence of 0.88% among those where BIS monitoring was not performed.[57]

Many anaesthetists simply do not believe these figures, because these incidences do not seem compatible with their own experience and practise. The problem with this is that few anaesthetists perform any sort of follow-up of their patients, and thus may never get to hear of possible psychological consequences that may have arisen. There is no reason to doubt the findings of the published studies on the incidence of awareness. I believe that awareness is a significant problem, that it is possible that many patients develop serious problems that do not reach the attention of medical personnel, and that it is a problem that deserves a lot more attention from the medical and scientific community.

Table 3.1 Classification of awareness (from Bailey and Jones)[53]

Category	Definition
1	Conscious awareness with spontaneous or prompted recall (explicit recall)
2	Conscious awareness with amnesia
3	Unconscious awareness with amnesia (Implicit recall)
4	No evidence of awareness

Table 3.2: Incidence of explicit awareness

Authors	Year	Awareness (%)	Dreams (%)	Sample size	Reference
Hutchinson et al	1960	1.2	3.0	656	[58]
Harris et al	1971	1.6	26.6	120	[59]
McKenna,Wilton	1973	1.5	-	200	[60]
Wilson et al	1975	0.8	7.7	490	[61]
Liu et al	1991	0.2	0.9	1000	[62]
Sandin et al	2000	0.18	-	11,785	[51]
Myles – BIS monitoring	2003	0.16	-	1227	[57]
Myles – no BIS monitoring	2003	0.88	-	1228	[57]

Chapter 4

Measuring anaesthetic depth

Given the problems that arise from our imprecise understanding of what anaesthesia is (or more correctly what anaesthesia is not), and what constitutes adequate anaesthesia, it follows that measurement of anaesthetic depth is also fraught with difficulty.

Clinical signs

Early methods of assessment of anaesthetic depth were of course based on observations of clinical signs. The efforts by Plomley, Snow and Guedel to define different stages of anaesthesia, mentioned in Chapter 2, also attempted to categorise clinical signs associated with each stage. More recently the "PRST score" was devised as an indicator of anaesthetic depth.[63] This score is based on systolic blood pressure, pulse rate, and the presence or absence of sweating and lacrimation, and although it does give an indication of anaesthetic depth it is not sufficiently reliable.

In general, these and other clinical signs that anaesthetists use to assess the adequacy of anaesthesia (such as pupillary size) are signs of sympathetic system activation, and are thus only surrogate measures of anaesthetic depth. Most of the signs are binary, and those that are not, generally do not correlate in a monotonic fashion with increasing depth of anaesthesia. None are specific to a single anaesthetic state -- for example no specific heart rate or pupil size reliably indicates the presence or absence of anaesthesia – and all are influenced by other factors such as drugs, hypoxia, hypercarbia and hypovolaemia.

In non-paralysed patients the response to verbal command or a noxious stimulus gives some information about the depth of anaesthesia prior to the stimulus. If the

patient fails to respond to command or fails to respond to a noxious stimulus then we assume that he or she is unconscious, and will fail to respond to a less noxious stimulus. We can also probably assume that the more severe the stimulus that has failed to elicit a response the greater is the depth of anaesthesia.

Of course, it is not usually possible to clinically assess the response to command in the paralysed patient. To circumvent this problem, Tunstall devised the "Isolated forearm test" [64] in which a forearm is isolated with a tourniquet prior to the administration of neuromuscular blocking agents. Thus during the operation, with the associated surgical stimuli, if the anaesthetic state is such that the patient is able to process verbal commands/questions, then he or she will be able to squeeze the hand of an observer in response to questions or commands. Using this technique Russell [52] and others [65] have found high incidences of conscious perception among patients "anaesthetised" with a benzodiazepine and opiate combination. The fact that many cardiac operations are still performed under high dose opiate and benzodiazepine "anaesthesia" leads one to conclude that many anaesthetists doubt the significance of conscious perception. There are other problems associated with the IFT, not least of which is that prolonged application of a tourniquet can lead to nerve injury, and so the test is rarely used in routine clinical practise.

As alluded to earlier there are pitfalls associated with the use of movement (in response to a noxious stimulus) as a marker of anaesthetic depth. The main problems are that no responses are possible in the paralysed patient, and even in the non-paralysed patient the sensitivity and specificity are poor (not all those who are conscious will move, whereas not all those who move are conscious).

Thus, while the traditional clinical signs of anaesthesia give clear and often binary endpoints, they are not reliable in giving an overall indication of anaesthetic

depth. Despite all the limitations and pitfalls of clinical signs, they remain the only available means of assessing anaesthetic depth for most anaesthetists in the United Kingdom. There is a need for a more reliable, objective (and preferably automated) method of assessment of anaesthetic depth. Several have been proposed in recent years, and some of these will be discussed.

Pupillometry

In every day practise anaesthetists use the papillary diameter to assess depth of anaesthesia. Pupillometers are machines that use infrared to measure the papillary diameter and assess the response to light flashes. Pupillary responses have been shown to correlate with the concentrations of some volatile anaesthetics,[66;67] but unfortunately the use of opioids limits the usefulness of the technique.

Oesophageal contractility

Evans and colleagues showed that increasing concentrations of inhaled anaesthetics agents reduced the tertiary (spontaneous non-propulsive) contractions of the lower oesophagus and proposed that lower oesophageal motility might be used to measure of depth of anaesthesia.[63;68] However, but the measured values depend on the anaesthetic agent used,[69] and the operation being performed.[70] The presence or absence of these contractions is an unreliable measure of anaesthetic depth and the method has not been accepted into routine practice.[69;71]

Heart rate variability - respiratory sinus arrhythmia (RSA)

Beat-to-beat heart rate variability (as measured from the interval between successive R waves on the ECG) gives an indication of autonomic function. It can be separated into high (>0.1Hz) and low (0.05 – 0.1) frequency components. RSA is the high frequency rhythmic change in heart rate (at the frequency of respiration). A measure of RSA has been shown to correlate with cerebral metabolism and the vagal outflow from the medulla oblongata.[72] It has been proposed as an index of anaesthetic depth [73,74] and incorporated in a commercially available monitor ("Fathom", Amtec Medical Systems Ltd, Antrim, UK). It has been compared with the BIS and SEF during induction of anaesthesia, but was found to have limited value due to the high incidence of apnoea, or hypopnoea during induction.[75] Further studies are needed to assess the usefulness of this measure.

EEG-based methods

The pioneer of electroencephalography is Richard Caton, of Liverpool, who demonstrated the presence of small electric currents in the brain in 1875. In the 1930's the development of electronic amplifiers enabled the recording of these currents (encephalography). Gibbs showed that anaesthetic drugs caused a shift from low voltage high frequency activity to high voltage low frequencies and postulated, in 1937, that the EEG might be used to measure anaesthetic depth.[76] Bickford was probably the first to use the EEG to monitor general anaesthesia.[77]

Early investigators described several characteristic morphologic patterns of waves in the EEG, occurring under different conditions – these are still used and referred to (Table 4.1). To the untrained, or non-specialist eye, the changes in the EEG during induction and emergence from anaesthesia are difficult to detect and interpret,

and the older EEG systems produced large volumes of paper (not welcome in the confined spaces of operating theatres). Thus there was a need for some form of automatic processing of the EEG, to compress the amount of data and yield information that was useful to anaesthetists.

Time domain analysis

The earliest methods of EEG analysis involved time domain analysis. At its simplest level the typical classification of waveforms shown in Table 4.1 is a form of time domain analysis. More sophisticated methods of time domain analysis includes analysis of changes in amplitude (voltage) or power (amplitude squared) with time. Generally this involves a statistical analysis of the amplitude or power – histograms can be drawn, and the mean and variance easily calculated.

In the 1950's Bickford noted that the EEG power changed during administration of thiopentone and ether and used a moving average of the EEG power to automatically control ether anaesthesia.[78] Later a commercially available monitor, the CFM (Cerebral Function Monitor) was developed, providing the user with a continuous trace of power over time. An improvement over the CFM was the Cerebral Function Analysing Monitor (CFAM), which performed a statistical analysis of the amplitude of the classical waveforms mentioned in table 4.1 and displayed the mean and the 10^{th} and 90^{th} percentiles of the amplitude of each. The CFAM was used to monitor depth of anaesthesia and sedation, and as a warning of cerebral ischaemia during carotid endarterectomy and cardiopulmonary bypass. Unfortunately both monitors are only sensitive to gross changes in anaesthetic depth or cerebral perfusion, and so are seldom used.

Zero crossing frequency is a time domain method that has been used to elicit average frequency information in the EEG signal, by calculating the frequency with which the EEG signal crossed the zero voltage level.[79] Naturally this method is fairly crude because higher frequency content in the EEG tends to be of lower amplitude – thus these waves, which are superimposed on larger lower frequency waves, will not cause the resultant signal to cross zero. **Aperiodic analysis** was developed in an attempt to refine the zero crossing technique – it involves wavelet analysis, where the amplitude is calculated as the difference between successive maxima and minima, and frequency from the time interval between them.[80]

Entropy is a mathematical description of the degree of complexity or chaos in a signal. [81] Numerous entropy statistics have been described. **Approximate entropy** quantifies irregularity in the time domain - the degree to which knowledge of previous amplitude values enables the subsequent value to be predicted. It has been shown to correlate with the end-tidal and calculated effect-site desflurane concentrations [82] and with the depth of sedation and anaesthesia.[83]

Other methods of time domain analysis involve analyses of the morphology of the EEG signal. One such method is the **Burst Suppression Ratio**,[84] which is used in the calculation of the BIS by a commercially available hypnotic monitor (Aspect Medical Systems, Newton, USA). In the BIS algorithm the Burst Suppression Ratio is the proportion of epochs in which the EEG is isoelectric.

Overall, time domain methods provide limited information, so that more complex analyses have been developed. Higher order methods require considerable computer processing power, and recent developments have only become possible with the recent improvements in computer technology.

Frequency analysis

Frequency analysis is an analysis of the component frequencies in a signal. To enable this analysis the signal must be transformed from the time domain into the frequency domain. This transformation is based on Fourier's Theorem which states that any complex waveform can be represented as the sum of a series of simple sine and cosine waves, each having a frequency which is a whole number multiple of the fundamental frequency, or slowest frequency found in the signal. This theorem was based on Fourier's studies of the conduction of heat in solid bodies, published in 1822.[85]

Prior to transformation, in modern systems, the signal is digitised, smoothed and filtered. Fourier transformation yields a series of pairs of coefficients each corresponding to a component frequency. The pairs are usually represented as complex numbers (having a real and an imaginary component), from which the power, and phase angle of each of the component frequencies can be calculated. The method most commonly used is the "Fast Fourier Transform."[86]

After transformation the resulting "spectral array" is often demonstrated graphically, typically as a graph showing frequency on the x-axis and power on the y-axis. The awake human EEG spectral array has a range of approximately 0.5 to 50 Hz (there is very little activity or power > 30 Hz). With changing levels of anaesthesia the spectral pattern changes. Although power generally shifts from the higher to the lower frequencies as anaesthesia depends, during sedation or "light" anaesthesia there may be an increase in the power in the high beta range.

The spectral array is sensitive to changes in the depth of anaesthesia, which is influenced by the brain concentrations of anaesthetic and sedative drugs (the product of administered doses and pharmacokinetic handling of the drugs), the patient's individual pharmacodynamic sensitivity to the administered agents, and the intensity of any

noxious stimuli. It is also influenced by factors that alter the cerebral metabolic rate (such as brain temperature, perfusion, and glucose levels).

To demonstrate the changes over time in the frequency spectrum, different graphical methods have been developed, of which two are commonly used. With the Density spectral array (DSA) time is typically plotted on the y-axis and frequency on the x-axis. At each co-ordinate (of frequency and time) the power is illustrated by a dot whose size or density correlates with the power. The Compressed spectral array (CSA) is a pseudo 3-dimensional line plot of power vs. frequency, where the plots at successive time intervals are stacked, so that peak and troughs of power appear as peaks and valleys. (Figure 4.1)

Graphical methods make it easier to recognise changes in the spectral array over time, but recognition of the characteristic spectral signatures (patterns of power vs. frequency) associated with different states requires training and experience. To simplify matters further simple mathematical/statistical methods can be used to summarise the frequency spectrum. The frequency spectrum can be divided into bandwidths – typically those corresponding to the classically described rhythms shown in Table 4.1 - and the total power in each bandwidth calculated. Other methods summarise the information contained in the whole spectrum in a single number or parameter. The median frequency (MF) is thus the frequency below which (or above which) 50% of the power in the EEG resides. The SEF represents the maximum frequency encountered, whereas the SEF95 is the frequency below which 95% of the power in the EEG is found.

With modern computers and signal processing techniques, the MF and SEF95 are fairly easy to calculate, and initially showed some promise as useful measures of anaesthetic depth. For example the SEF95 was shown to correlate with some signs of anaesthetic depth [87] and with the concentration of hypnotic,[88] and the MF was used to

control closed-loop administration of propofol,[89] methohexitone [90] and alfentanil.[91] However, there are several problems limiting the usefulness of these parameters. Firstly, these parameters only represent a statistical summary of the spectral array. They do not necessarily vary monotonically as anaesthetic depth increases, and significant changes in the array can occur with little change to the MF or SEF. During lighter levels of anaesthesia, when there may be an increase in power in the high beta range, the MF and SEF may not change or may actually increase before later decreasing. For this and other reasons there is considerable overlap in the values found in different clinical states.[75;92;93] Thus while a SEF of 16 Hz has been shown to be 100% specific for loss of consciousness, it is only 9% sensitive.[92] Another problem with frequency-based EEG analysis is that the Fourier Transformation cannot characterise burst suppression, so that the MF and SEF become unstable and may show paradoxical increases at the onset of burst suppression.

Spectral entropy quantifies the irregularity in the frequency domain of a signal, and is incorporated in a commercially available anaesthetic depth monitor (M-Entropy, Datex-Ohmeda, Finland).[94] Although it appears to be a promising measure of anaesthetic depth, at present there are few published validation studies.

Evoked potentials

All the methods of EEG analysis discussed until now have involved analysis of spontaneous EEG. Evoked potentials, as the name suggests, are potentials measured at the cortex, but evoked by a stimulus (auditory, visual or somato-sensory).

The transient auditory evoked potential (AEP) is the most common evoked potential used for assessing depth of anaesthesia. After an auditory stimulus a series of

electric waves reach the cortex – different peaks and troughs arise from different electrical events along the auditory pathways. Because the amplitude of the signal reaching the cortex is very small (much smaller than the background EEG) specialised signal processing techniques are used to extract the signal from the background EEG – usually this is done by applying repetitive stimuli, and averaging a large number of recordings (sweeps) between successive stimuli, thereby cancelling out the virtually random background noise.

The early latency part of the signal (0 to 20ms after the stimulus) reflects passage through the brainstem, and is relatively unaffected by anaesthetic agents. Individual waves are conventionally numbered with roman numerals I to VI. The middle-latency or early cortical portion (20 to 100 ms) reflects the passage through the midbrain and thalamus to the auditory cortex, and is the part of the signal of most interest during anaesthesia (as anaesthesia deepens the amplitude of the specified waves decreases whereas the latency increases). By convention the successive troughs in this portion are labelled N0, Na and Nb respectively, and the peaks P0, Pa and Pb. Finally the long-latency or late cortical portion (>100ms) reflects the pathways between the auditory cortex and association areas, but this portion tends to disappear at even light levels of anaesthesia.

For transient AEPs the stimuli are applied at a frequency of approximately 7 Hz, so that a sweep duration of ~144ms is possible between stimuli. Early work showed that there was good separation between the Na and Nb latencies found during periods of consciousness and unconsciousness;[95,96] that the Na latency has a linear correlation with the blood propofol concentration, [96] and that the Nb latency can be used to predict likelihood of recall.[97] Unfortunately, automatic measurement of latency and amplitude is difficult. To enable online, real-time analysis of the AEP waveform, Kenny and

Mantzaridis developed an AEP index. This index is derived from a mathematical analysis of the morphology (essentially the "curviness") of the wave, and thus reflects both changes in latency and amplitude. [98] The AEP index has been shown to be effective at detecting the transition from unconsciousness to consciousness.[92] The A-line®, a commercially available AEP monitor (Danmeter A/S, Odense, Denmark) uses an ARX model (autoregressive model with an exogenous input) to rapidly extract the AEP signal, from which the AAI (A-Line ARX Index) is calculated using a similar mathematical method to that used to calculate the AEP index. The AAI has recently been shown to correlate well with depth of sedation and loss of consciousness, although there is a broad overlap between values found during consciousness and unconsciousness, and in common with other measures of anaesthetic depth it was unable to predict response to noxious stimuli. [99]

Higher frequency stimuli are used to generate steady state AEPs (typically 40 to 60 Hz) so that the potentials arising from successive stimuli become superimposed to generate a large amplitude stable response.[100] A coherence index (CI) has been derived to describe the stimulus frequency at which maximum power in the signal was found; and this CI has been shown to correlate inversely with cognitive function and psychological performance in volunteers undergoing sedation with propofol and isoflurane. [101;102]

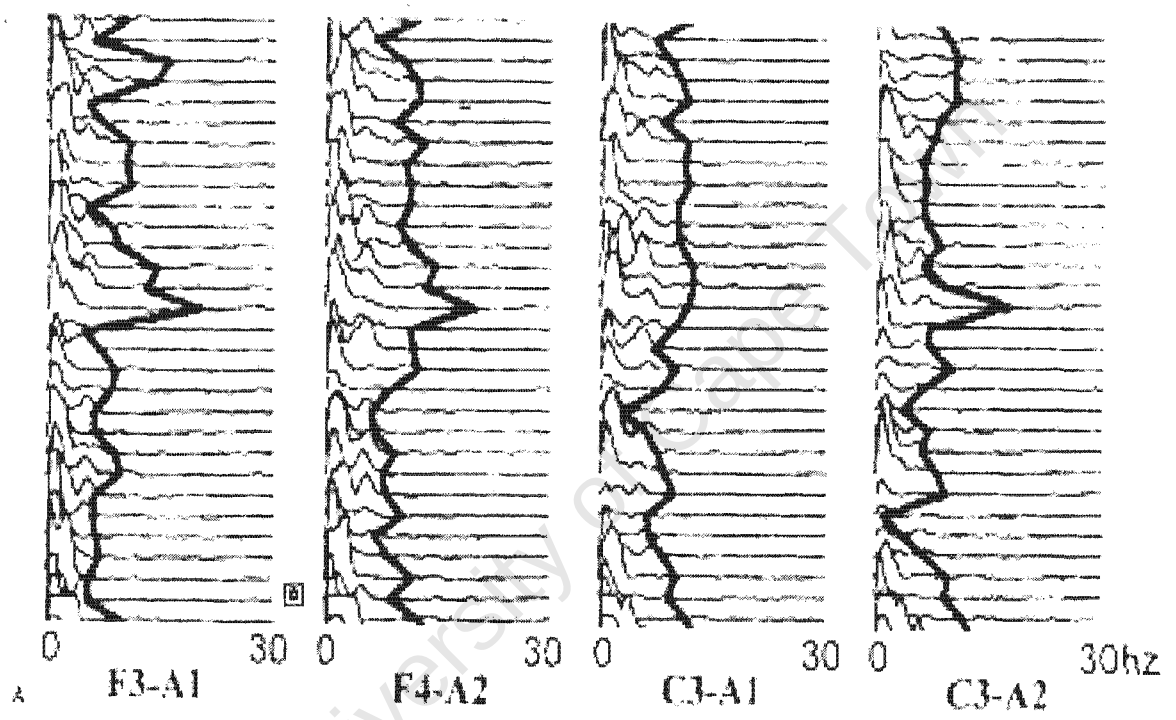
Bispectral analysis

Bispectral analysis is higher-order method of analysing the spontaneous EEG, used in the calculation of the Bispectral Index, which was used or recorded in several of my research projects. It is thus covered in greater detail in a separate chapter (chapter 10).

Table 4.1: Typical classification of EEG patterns

	Frequency (Hz)	**Amplitude (μV)**	**Conditions**
Delta	0.3 – 3.5	100	Sleep, anaesthesia
Theta	4 – 7	10	
Alpha	8 – 13	20	Augmented by closing eyes, mental repose. Reduced by visual and mental activity
Beta	14 – 25	20	May indicate pain
Gamma	> 26	10	Rare

Figure 4.1: Compressed spectral array of an anaesthetised patient. Four channels of data are shown. Each line represents the spectrum at a moment in time, with more recent data at the bottom. Frequency is represented on the x-axis, and power in a pseudo third dimension: the heights of the peaks (coming out of the page) are proportional to the power. The thick bold line represents the median frequency.



Chapter 5

Sedation, and measurement of sedation

With increasing doses of anaesthetic drugs there is progressive loss of psychomotor function, followed eventually by loss of consciousness, with progressive loss of airway and other reflexes. The distinction between sedation and anaesthesia thus depends on how loss of consciousness is defined. From a safety point of view it is best to consider loss of consciousness to have occurred when the subject ceases to respond to voice, as opposed to endpoints that usually occur after a further delay (such as loss of the eyelash reflex). This view was endorsed by the report of the Joint Working Party of the Royal College of Radiologists and Royal College of Anaesthetists, published in 1992, which stated that sedation should be defined as a state of depression of the central nervous system "during which verbal contact with the patient is maintained".[103]

Various clinical sedation scoring systems have been developed in an attempt to quantify or measure the degree of sedation. In the critical care setting they are used to titrate sedative agent administration and to provide a record of sedation status. Commonly used scales include the SAS (Sedation-Agitation Scale),[104] Cook, [105] and Ramsay. [106]

The critical care scoring systems are not particularly useful in non-ICU settings - their focus is on patient comfort, and issues affecting ease of care and ventilation such as restlessness and agitation. The Observer's Assessment of Alertness/Sedation scale (OAA/S), described by Chernik, [107] has been carefully validated and is often used in anaesthetic research. Typically the responsiveness score of the OAA/S is used (Table 5.1) but it should be remembered that a score of less than 3 represents anaesthesia rather than sedation. Steward developed a scoring system for assessing sedation in the

recovery room. [108] Robertson developed a modified version of the Steward scoring system to assess the effects of doxapram on arousal from anaesthesia, [109] as did Irwin who used it to assess sedation levels in patients using a patient-controlled sedation system.[110] Separate assessments of consciousness, airway maintenance and activity are made, and the scores added (minimum 0, maximum 9). Patients who respond to command will score between 7 and 9 points.

Existing scores, described above, are all poor at identifying different degrees of sedation. Anxiety, being an emotion, is even more difficult to assess and quantify. The best person to assess the degree of anxiety is of course the person experiencing it, and to this end visual analogue scores and ordinal or categorical scoring systems are often used in clinical studies (e.g.: patients can be asked directly how much anxiety they are feeling: this could be categorised as none, mild, moderate, severe or extreme).
In day-to-day practise sedation and anxiety scoring systems are seldom used, and physicians who are administering sedative or anxiolytic agents tend to make subjective assessments of the efficacy of their treatment. This is very difficult to do accurately, even when the level of distress or anxiety experienced is constant. [111] Patients may hide or understate their feelings, and some sedative agents may cause sedation without anxiolysis, thus masking the level of distress. When patients are sedated for a procedure, the level of distress will change during the course of the procedure. The physician who administered the sedative should continuously assess to patient to assess the effectiveness of the sedative and to observe for serious side effects such as loss of consciousness and loss of airway reflexes. In many settings, the physician who administers the sedative agents is also the one who is performing, and thus distracted by, the procedure. Often the responsibility for observing the patient is delegated to non-medically trained personnel.

Similar problems have been found with assessment of pain, and this has lead to the development of patient-controlled analgesia (PCA) systems, which have proved to be popular with patients and clinicians alike. Similarly, patient controlled sedation systems have been developed to overcome the difficulties with objective assessment of sedation and anxiety – based on their personal experience of these emotions over time, the patient is able to implement an individualised sedative dosage regimen. This has the potential for increased patient satisfaction, along with improved safety.

The Bispectral Index, discussed in greater detail in chapter 10, is a useful objective measure of sedation, and is currently the only EEG-based parameter to have been proven to accurately correlate with depth of sedation, and the likelihood of memory formation.

Table 5.1

Responsiveness scores of the modified Observer's Assessment of Alertness/Sedation Scale [107]

Score	Responsive
5	Responds readily
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

Chapter 6

Conclusion

The early anaesthetic agents were far from ideal in terms of adverse effects, potency, speed of onset and duration of clinical effects. However, the simple (inhalational) methods of administration of these agents provided a degree of feedback control and thus some protection against under- and overdosage.

Later developments in anaesthetic practise, such as the ability to administer drugs intravenously and the discovery of neuromuscular blocking drugs did, on the whole, improve safety, but they also removed some of this feedback. The more recent development of automated, objective measures of sedation and anaesthetic depth, coupled with developments in computer technology and control theory, have made feedback computer control of sedation and anaesthesia possible. At a less "high-tech" level, development of patient-control technology has meant that patients can self-administer analgesic or sedative agents, thereby forming a feedback system for which they determine the set point themselves based on the pain or anxiety experienced, the desired level of sedation and the individual patients' tolerance of the adverse effects of the agent in use.

Development of a BIS data management and closed loop control system

Chapter 7

Introduction

Whilst working at the Glasgow University Department of Anaesthesia, I conducted several studies that form part of this thesis, and for which it was necessary to automatically record the Bispectral Index (BIS). In some of these studies I used the BIS as the control variable for a computerised system that would automatically control a propofol infusion.

At the time, there were no readily available computer programs able to implement closed loop control of anaesthesia using the BIS. Although, a newer version of RUGLOOP that had closed loop functionality was being developed, this version was a prototype, and was not freely available. Our department had an AEP-based closed loop anaesthesia system, but it could not be adapted to use the BIS as the control variable. This was because the AEP system was old, platform specific (it could only run on a specific Toshiba 286 laptop model), could only run under DOS, not in Windows, and although much of the software was written with Turbo Pascal (with which I was familiar) many of the software routines were written in Assembly Language (of which I had very little understanding or familiarity). Moreover the system and the software were the intellectual property of another member of the department.

It thus became apparent that it was necessary to produce a completely new system, capable of performing these, and other functions. As the system had to be capable of closed loop control of anaesthesia, control theory will be discussed in the next chapter. The process of developing the system will be discussed in the following chapter.

Chapter 8

Control theory

Man has always tried to control his environment. Control systems are known to have existed for many millennia. Systems able to control irrigation in Mesopotamia are thought to have existed by the 20th century BC. Nonetheless it was only in the 19th century AD that the first theoretical analysis of a control system was performed and published, when James Clerk Maxwell produced a differential equation model of the Watt governor.

The two basic types of control systems are feedforward and feedback (also referred to as open loop and closed loop respectively). The oldest systems were generally feedforward systems – these are systems in which no information from the process being controlled is used to correct the input to the process. A simple example is a loom controlled by a set of punch cards programmed to control the patterns being woven. Feedback control systems are systems in which information from the process being controlled is used to correct the input to the process. Until World War II most feedback control systems were single loop, in which feedback and correction were provided once, from a single point in the process.

The advent of analogue and then digital computers enabled more complex control, with feedback and correction from multiple points, and control of multiple aspects of processes (e.g. control of temperature and pressure of chemical reactions). This lead to the development in the 1950s of "Modern control theory," a field of applied mathematics that is described in the Encyclopaedia Britannica as "that branch of system theory concerned with changing the behaviour of a given complex system by external actions."

The essential components of a feedback control system (summarised in Figure 8.1) are:

- An observable and controllable system
- A control actuator able to influence the state of the system
- A control variable that should accurately reflect the state of the system
- A set point for that variable that can usually be altered by the user
- A control algorithm to determine what alterations should be made to the control actuator based on the error between the measured value of the control variable and the set point.

The common types of control algorithm are:

1. On-off
2. Proportional
3. Proportional-integral
4. Proportional-derivative
5. Proportional-integral-derivative

To illustrate the principles of these control algorithms I have run some simple simulations using Microsoft Excel® (see Figs 8.2, 8.3, 8.4 and 8.5). In the simulations the control variable is a hypothetical, real-time measure of anaesthetic depth (no processing delay). In each simulation the same set point profile is used. For the control actuator a blood concentration targeted propofol infusion is used, with the assumption that propofol pharmacokinetics can be adequately described by a single compartment model. Arbitrary values for the elimination rate constant and for k_{e0} (the rate constant that describes effect-site equilibration) have been used. The control actuator used in these simulations, and indeed any drug infusion system, is an asymmetric controller –

drug can be infused at any rate within the technical limits of the infusion pump, whereas the rate of movement of drug out of the blood is dictated by concentration gradients between tissue compartments and by the efficiency with which the drug is metabolised in an individual patient.

On-off control

On-off control is the simplest type of control algorithm. With on-off control only two inputs to the system are possible: "on" (maximum power/input) and "off" (no input). This type of control system is common in domestic appliances, an example being the thermostat in an oven. If the temperature is below the set point power is applied to the heating element, and when the temperature is above the set point no current is supplied to the element. To prevent rapid on-off cycling there is usually a difference between the turn-on and turn-off temperatures, known as the "hysteresis". Turn-on usually occurs slightly below the set point, whereas turn-off is just above it. This type of algorithm inevitably leads to some oscillation in the control variable.

Proportional control

Proportional control is illustrated in Figure 8.2. With proportional control, the system adjusts the input to the system (i.e. the control actuator output) in proportion to the error (the difference between the actual value of the control variable and the set point). Mathematically this can be represented as follows (where K_p is the gain constant):

$$\text{Input}(t) = K_p \times \text{Error}(t)$$

After a change in set point the speed with which the actual value of the control variable will approach the new set point will depend on the gain constant. The same applies when an external perturbation causes an increase in the error. At lower values of the

gain constant, the control variable will increase or decrease slowly, approaching the set point asymptotically. As the gain constant is increased the response rate will increase, until eventually the system will become underdamped and unstable with oscillations. At maximum gain in a system where control is asymmetrical (as in the oven example where the heating element can only add, not remove heat), the controller will perform in the same manner as an on-off controller.

With tuning it is possibly to find an optimal value for the gain constant, associated with optimal damping – following a change the system will approach the new set point rapidly, overshoot only once or twice and then have small oscillations above or below the set point.

Proportional-derivative control

The problem of oscillation that occurs at higher values of the K_p can be overcome by adding a derivative factor to the control algorithm. Proportional-derivative control is illustrated in Figure 8.3. The derivative factor allows the algorithm to take account of changes in the magnitude of the error – as the control variable approaches the set point, the absolute value of the error decreases. To avoid under- or overshoot, the algorithm will cause an increase or reduction to the input (depending on whether the control variable is approaching the set point from above or from below). Mathematically this can be represented as follows (where K_p is the proportional gain constant, and K_d the derivative gain constant):

$$\text{Input}(t) = Kp \times [\,\text{Error}(t) + (Kd \times \frac{d}{dt}(\,\text{Error}(t) - \text{Error}(t-1))\,]$$

An increase of the derivative gain factor increases the damping. With an asymmetric control actuator, however, there may be a threshold value beyond which an increase in K_d will have the opposite effect. This is illustrated in Fig. 8.3: when K_d is increased to

3.0, and when the depth of anaesthesia is approaching the set point from below there is no overshoot, whereas when it is approaching the set point from above there is marked undershoot. This is because at the moment when the set point is reduced the algorithm reacts to the sudden large increase in error by causing a large increase in blood propofol concentration. After that the algorithm detects that the error size is reducing, and reduces the target blood concentration, but the blood concentration falls more slowly, it's rate of fall being limited by the rate of elimination. By the time the blood concentration has reduced sufficiently, the brain concentration has risen too far, causing an excessive depth of anaesthesia.

Proportional integral control

At lower K_p values the problem is that the control variable approaches the set point asymptotically (and theoretically never reaches it). Under steady state conditions this will give rise to a constant bias, or offset. The addition of an integral factor to the control algorithm can attenuate this (Fig 8.4), and make the system respond more rapidly to errors, without causing oscillation. If the integral gain factor is too high then some overshoot and undershoot will occur. Mathematically proportional integral (PI) control is described thus (where K_i is the integral gain constant, and *a* the time interval over which historical errors are summed):

$$\text{Input}(t) = Kp \times \left[\text{Error}(t) + Ki \times \int_{t-a}^{t} \text{Error}(t)\, dt \right]$$

Proportional integral derivative control

Most automated methods of measuring anaesthetic depth involve a processing delay, and are susceptible to artefact and noise. Random changes may thus lead to sudden,

short-lived fluctuations in the control variable. A large derivative gain constant is thus undesirable because these fluctuations will cause large, unnecessary changes to the control actuator. Optimal control (rapid response, with minimal oscillation) can thus usually be achieved with an algorithm containing proportional, integral and derivative components (Figure 8.5).

Other types of control algorithm

Non-fixed gain constants and self-tuning systems

Classical PID control algorithms described above are usually fixed-constant systems in which the constants "tuned" at the development stage to suit the average situation or subject. The methods of "tuning" the gain constants for optimal efficiency are beyond the scope of this text. Usually the system is tuned to suite the average subject from the population. However, superficially similar subjects or patients will respond differently to similar inputs from the control actuator – human subjects exhibit a large degree of inter-individual pharmacokinetic and pharmacodynamic variability. Fixed-constant PID algorithms do not take account of these differences. As a result a patient who is very sensitive to the effects of a drug may display excessive oscillation of the control variable, whereas in others the system will appear to respond slowly to changes.

Systems have been developed in which the gain constants can be altered at runtime, during the control process. The simplest of these systems allow the user to alter the gain constant while the program is running. Other, more sophisticated systems have algorithms that allow learning or self-tuning – the system "learns" about the sensitivity of the individual subject and tunes the gain constants automatically.

Model-based systems

Model-based systems develop a model to explain the behaviour of the subject, and then use the model to make control decisions. A recent and successful example is the closed loop anaesthesia system developed by Struys and de Smet.[112] This system uses the BIS as the control variable to automatically control an effect-site targeted propofol infusion, using a model-based adaptive controller. During induction of anaesthesia the system increases the target propofol concentration in a step-wise open loop fashion, and records the corresponding BIS and propofol concentration values. This enables the system to develop an initial pharmacodynamic model – from which the parameters required to plot a typical sigmoidal E_{max} curve (a "Hill curve") are calculated. Once anaesthesia is induced and the target BIS value is reached, the system reverts to automatic control and the propofol concentration required to produce the desired BIS value is read off the curve. As conditions change, and additional stimuli are introduced or withdrawn, the pharmacodynamic relationship changes. For a given propofol concentration the BIS may be higher or lower than before. The system is able to detect these changes and update the position of the Hill curve, to enable the required propofol concentration to again be read off the curve (Figure 8.6).

Fuzzy logic

Classical set theory only allowed for two degrees of membership of a set: full or none. The work of Lukasiewicz (in the 1920's) and Black (in the 1930's) introduced the concept of multivalued logic to statements (i.e. truth values between zero and one) and to sets.[113] In 1965 Zadeh coined the term "fuzzy sets" to describe sets in which individual elements may have differing degrees of membership. This lead to this field of mathematics being named "fuzzy logic." In some ways fuzzy logic is very similar to

human reasoning – few humans make decisions based on mathematical formulae, but rather base their decisions on more complex, "fuzzy" reasoning. This new branch of applied mathematics holds great promise for the future.

The first step in designing a fuzzy logic controller is to define *fuzzy sets*. For example when designing a system for control of a propofol infusion for surgical anaesthesia based on BIS measurements, a series of sets of BIS values may be developed. These could be called "Too high," "Too low" and "Adequate." A BIS of 60 may be a member of more than one set – it may have 10% membership of the set "Adequate", whilst having a 20% membership of the set "Too high". A series of sets of possible changes to the propofol infusion could also be constructed. These could be called: "Small changes", "Medium changes" and "Large changes." A target concentration change of say, 0.5 μg/ml could well have membership of all three sets.

Next a set of *fuzzy rules* has to be developed – for the current example rules may include the following: (1) if the BIS is too high for surgical anaesthesia, and the propofol concentration is very low, make a large change to the propofol infusion rate; (2) if the BIS is adequate for surgical anaesthesia, do not change the propofol infusion rate; (3) if the BIS is too high and the propofol concentration is average, then make a moderate change to the infusion rate. In this example, one BIS value will trigger more than one rule, each with a different outcome. The final step is "*defuzzification*" in which the outcomes of the different rules are combined, and then converted into a finite decision – in this example the exact new propofol infusion rate or concentration.

Fuzzy logic has many day-to-day applications – fuzzy logic controllers are used to control many household appliances, industrial processes and even underground rail networks. [114] In the medical sphere fuzzy logic controllers have been used for automatic control of muscle relaxant administration.[115]

Neuro-fuzzy systems

Neural networks are capable of "learning" from historical data, and are particularly efficient at pattern recognition. Typically they are trained on historical data, and then used to recognise patterns in new data. Most medical applications so far have involved diagnostic processes, [116-118] but Veselis used neural networks to predict, with reasonable accuracy, depth of sedation of intensive care patients, and even the drug used for sedation, based on the patterns found in the electroencephalogram.[119;120] Neural networks, used in combination with fuzzy logic controllers, so-called "neuro-fuzzy" systems have huge potential for future use in closed loop control systems.

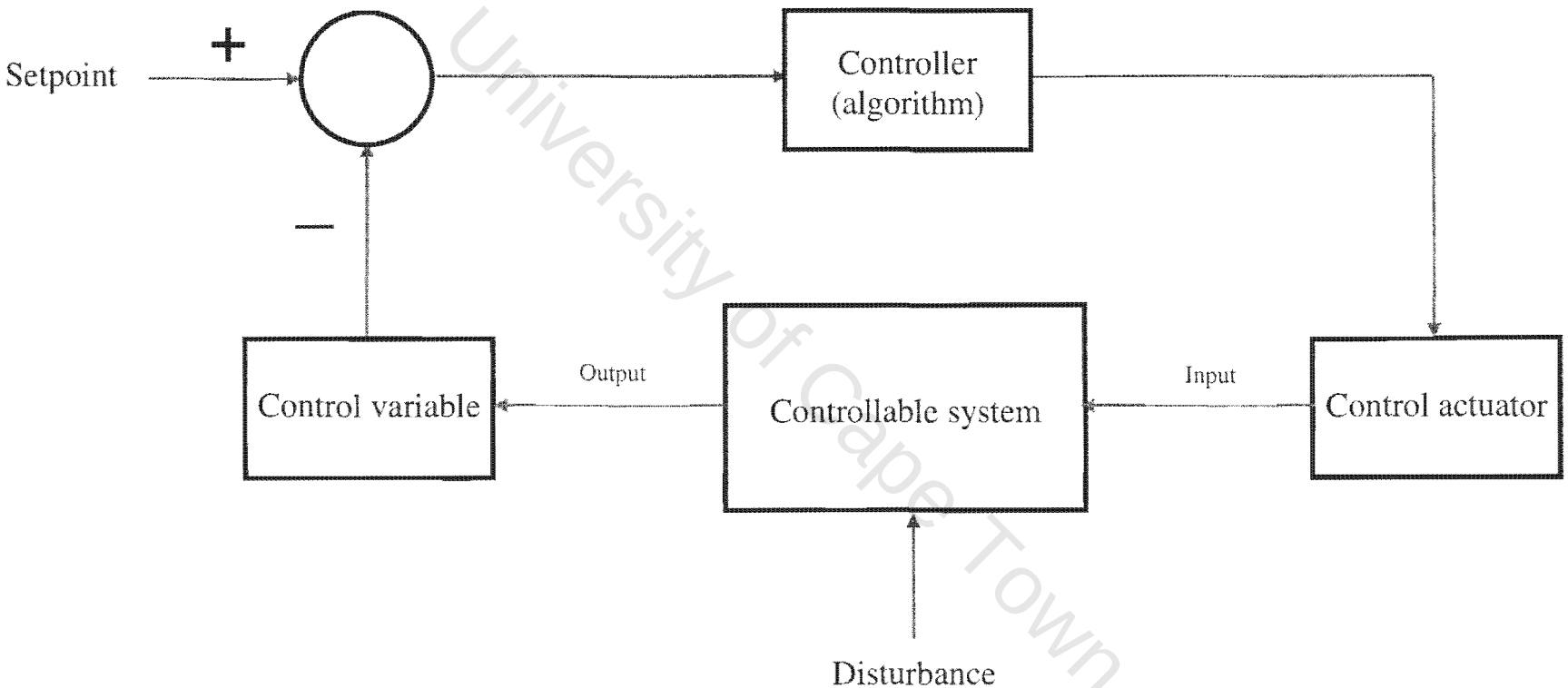


Figure 8.1: Basic components of a closed loop system

Figure 8.2: proportional control. If the proportional gain constant (k_p) is a low value the system is slow to react to error, whereas if the gain is high, there is overshoot and oscillation

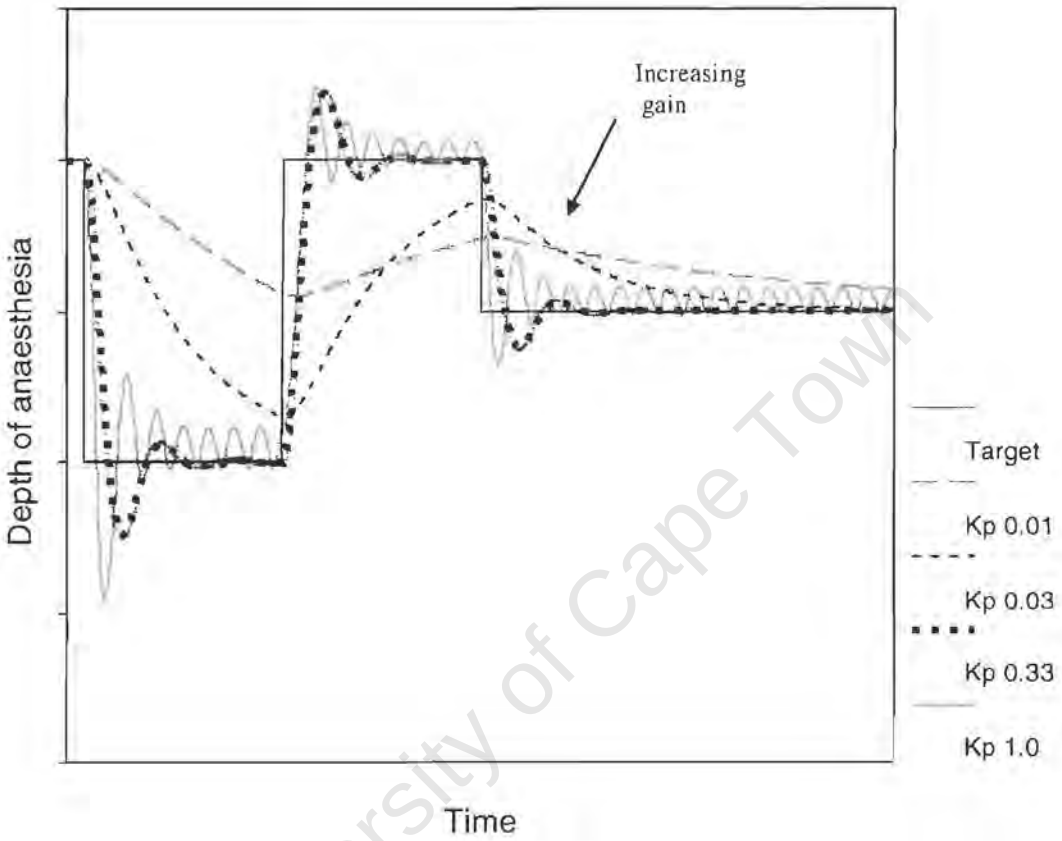


Figure 8.3: proportional-differential control. In this simulation the proportional gain constant has been set to 1.2. Thus when the differential gain constant (k_d) is zero there is considerable oscillation. Control improves significantly as the k_d is increased. In this example the most accurate control is achieved with a k_d of 1.0. Above this value control is more accurate when the control value is approaching the set point from below, but less accurate when approaching the set point from above, when there is marked overshoot.

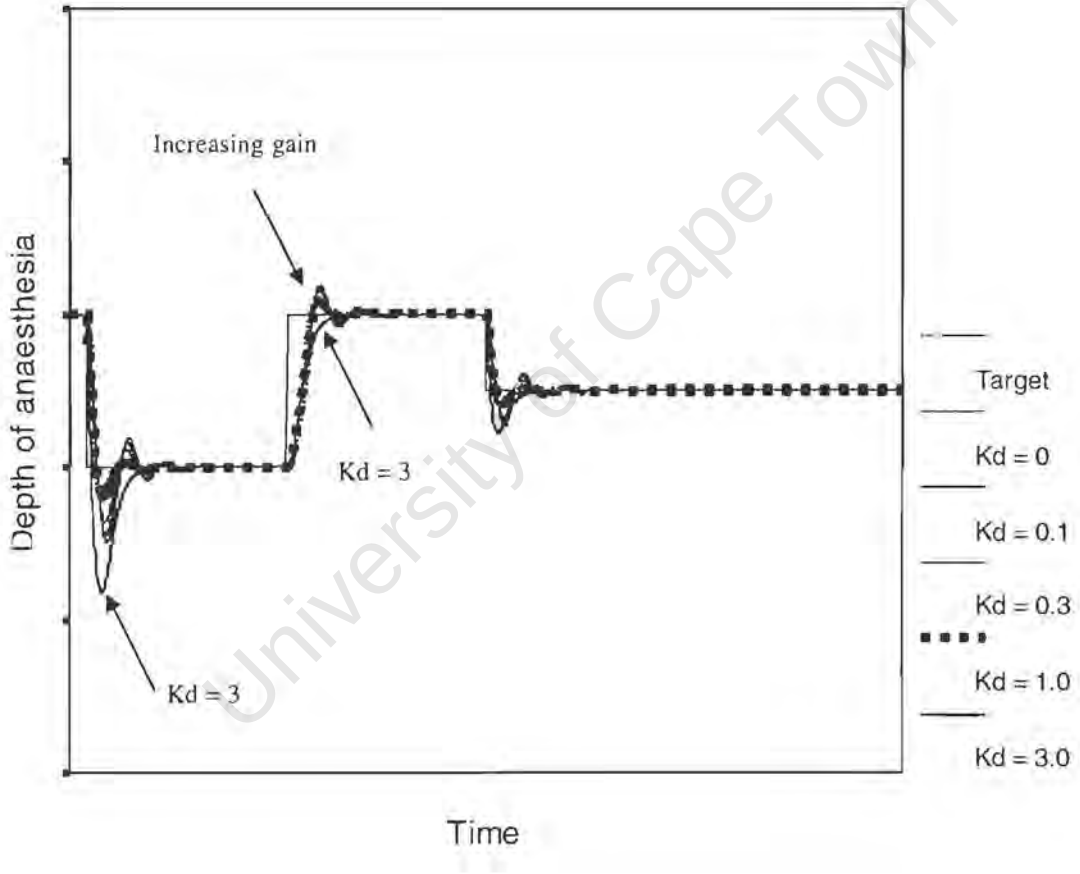


Figure 8.4: proportional-integral control. In this simulation the proportional gain constant has been set to 0.03. Thus when the integral gain constant (k_i) is zero there is a very slow response to error. Control improves significantly as the k_i is increased. In this example the most accurate control is achieved with a k_i of 1.0.

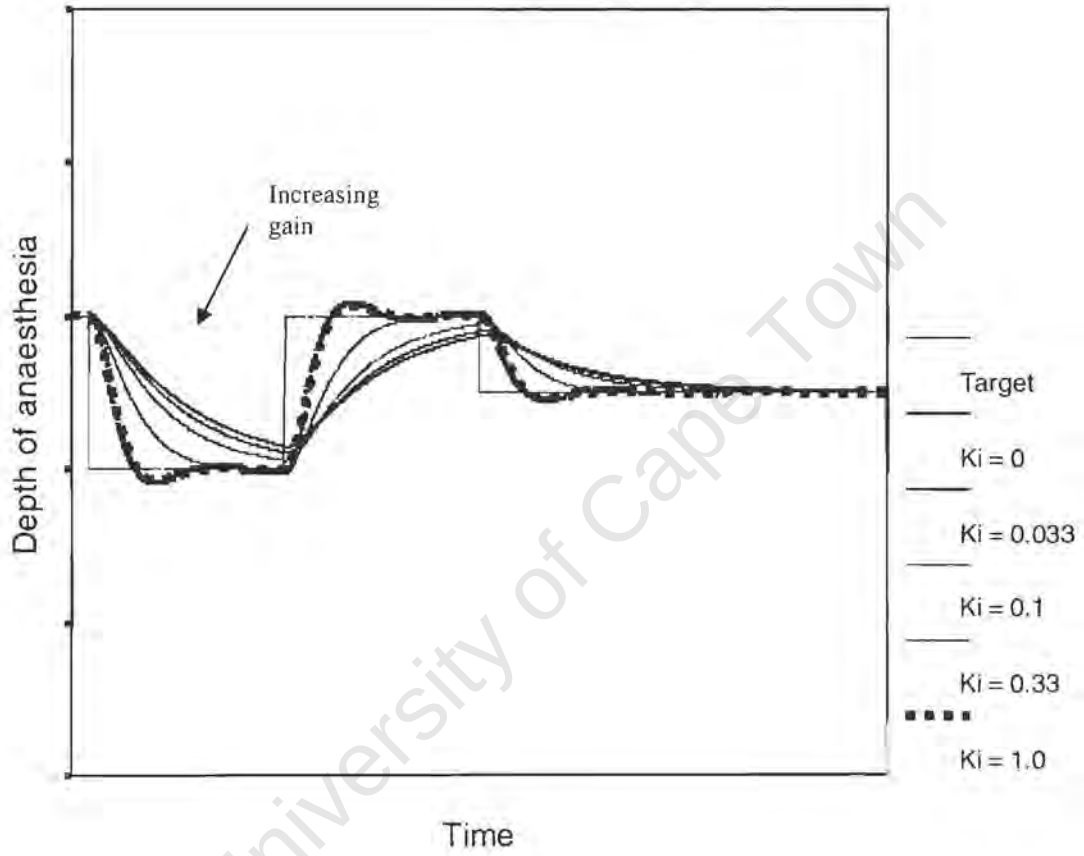


Figure 8.5: proportional-integral-differential control. By adding an integral and a differential factor, speed of response is improved, without overshoot and oscillation are minimised. In this simulation optimal control is achieved with k_p 0.7, k_d 3.0 and k_i 1.0. Note that the Y-axis scale has been expanded from that shown in previous figures.

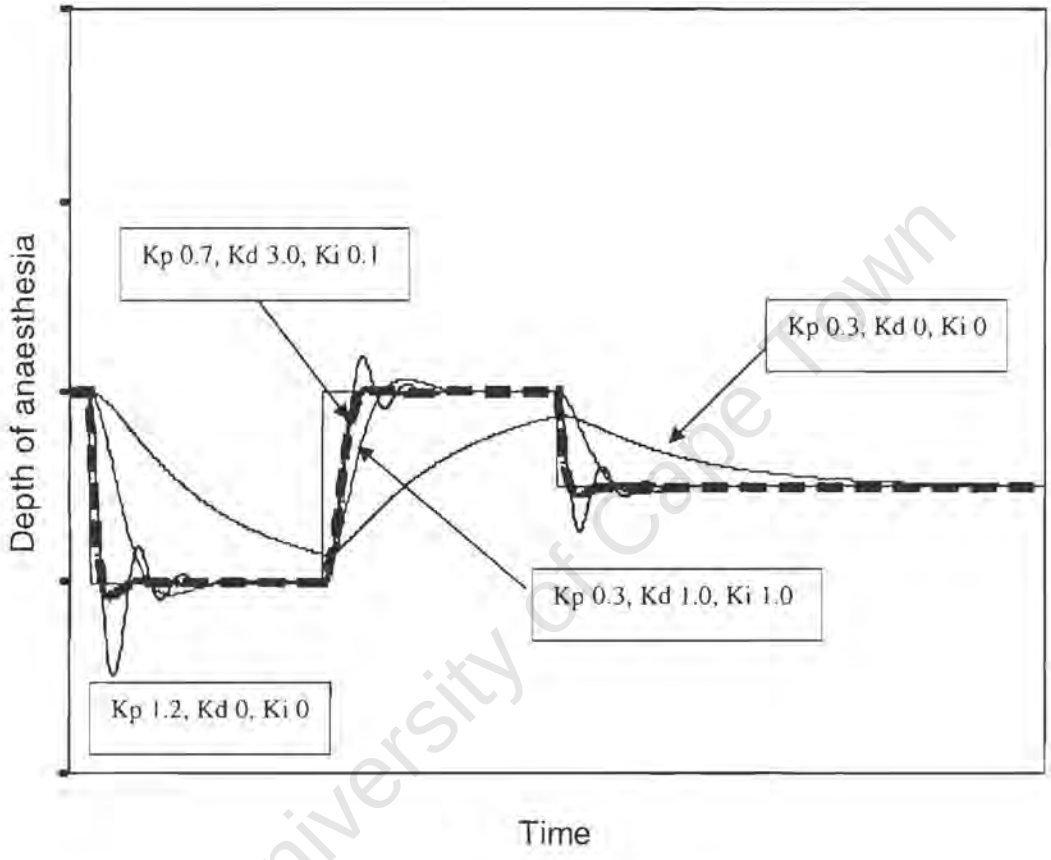
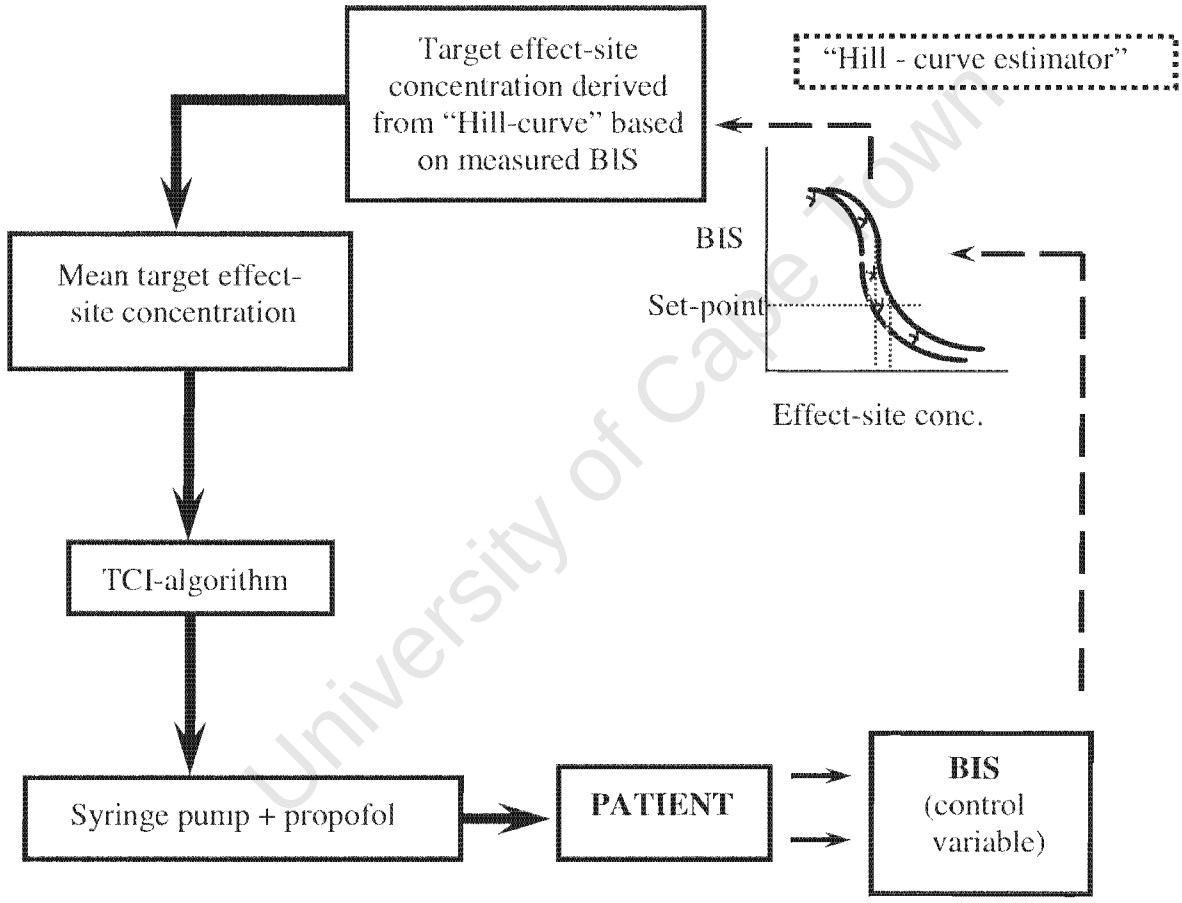


Figure 8.6: Schematic of the BIS-guided model-based controller developed by Struys et al (diagram adapted from that drawn by Struys, with permission). [112] The initial Hill curve is drawn during open loop induction of anaesthesia. Once the set-point of the control variable has been attained closed loop control is initiated. A surgical stimulus will cause the BIS to rise above the set-point – the curve is re-drawn and the required propofol concentration to achieve the set-point is read off the graph.



Chapter 9

Project 1: **Development of a BIS data management and closed loop control system**

As mentioned in the introductory chapter to this section, my first project was to design and develop a system that was capable of performing one or more of the following functions:

- Communication between a personal computer (PC) and BIS monitor, to enable display and electronic storage of time-stamped EEG variables
- Communication between PC and propofol TCI infusion system, to enable display and electronic storage of propofol concentrations along with the EEG variables
- Manual, mouse or keyboard-based control of the propofol TCI system
- Automatic closed-loop control of the propofol TCI system

Methods

The overall process can be summarised as follows:

- A set of design objectives was established.
- The necessary hardware was assembled
- Separate program tasks were identified, then written, tested and debugged, individually
- The function of the whole system was then tested prior to use in patients

GENERAL DESIGN OBJECTIVES

Hardware

- All components had to be modern, low cost and readily available
- System to operate on a laptop personal computer
- Components to be lightweight and portable
- Components to be sufficiently robust to function in the operating theatre environment – i.e. able to function in an electrically noisy environment, connections between devices to be secure
- All components to have back-up power supply in the event of mains interruption
- All devices to conform to British standards for electrical safety

Software

- All software had to be developed in-house (by myself)
- System able to function in the following modes of operation (with easy inter-changeability between modes)
    a. "Monitor-only mode": acquisition, display and electronic storage of EEG variables
    b. "Manual mode": above functions plus manual control of propofol infusion
    c. "Automatic mode": all above functions plus automatic control of propofol infusion
- Safety to be paramount
    a. Continuous checking of integrity of communications between devices
    b. Routines to deal with communications failures
    c. Audible and visual alarms to warn of problems

d. Immediate manual override of propofol infusion possible at all times – either from the PC or using the dials of the TCI device independently of the PC

e. Automatic absolute minimum and maximum propofol concentrations

f. Propofol infusion to continue running even in the event of complete failure of all other systems

- User interface

a. Modern, clear display of all important information

b. All important information on a single screen

i. Numerical display of current BIS value

ii. Numerical display of current target and actual (estimated) propofol concentrations

iii. Graphical display of previous BIS values (trend)

iv. Graphical display of previous propofol concentrations

v. Graphical display of target BIS value (automatic mode)

vi. Continuous display of system status

vii. Immediate and obvious display of error messages

c. Controls – controllable from:

i. Keyboard: typing of numbers or shortcuts for other functions

ii. Mouse control of buttons and dials

iii. Suitable for use with touch-sensitive screen

- Data storage

a. Real-time, time-stamped data storage

b. Data to be recorded:

i. EEG variables

ii. Status and error variables

iii. Blood and effect-site propofol concentrations

c. Data to be stored in an easily accessible format, suitable for data manipulation

HARDWARE

Personal computer

An Acer laptop PC (Acer 313T, Acer Inc., Taiwan ROC) was chosen because it weighs only 2.2 kg, and at the time the specifications were state-of-the-art: motherboard speed 260 MHz, RAM 64 MB, hard drive storage space 2 GB, colour backlit monitor, finger pad mouse. The operating system is Windows 98. One limitation of the PC was that it only had one serial port available for use (the other was dedicated to the modem), whereas two were required – one for communication with the BIS monitor and the other with the TCI system. This problem was solved by the purchase of a PCMCIA adapter card (DSP-100, Quatech, OH, USA) that provided two further serial ports.

BIS monitor

The control variable for the system is the BIS. Initially this was obtained from an Aspect A-1000™ monitor, and latterly from an Aspect A-2000™ monitor (both on loan from Aspect Medical Systems International BV, Leiden, The Netherlands). These monitors are approved by the United States Food and Drug Administration, and have satisfied the stringent European Union safety requirements as a medical device.

The A-1000 monitor requires a montage of 4 self-prepping silver-silver chloride electrodes (Zipprep™, Aspect Medical Systems, Newton, MA, USA) applied at AT1, AT2, FpZ (reference) and Fp1 (ground). This configuration provides four channels of data – the BIS value displayed by the monitor being the mean. The A-2000 monitor

uses a strip of 3 electrodes (available from Aspect Medical Systems), applied at AT2, FpZ and Fp2. This configuration provides two data channels. Both monitors are stand-alone, but have an "off-monitor" amplifier close to the patient. Short electrical leads connect the electrodes to the amplifier (typically attached to the patient pillow by a clip), and a cable connects the amplifier to the monitor.

Both monitors calculate BIS, burst suppression ratio, spectral edge frequency (SEF), EMG power and a signal quality index. The A-1000 also calculates median frequency (MF) and the absolute and relative power in the α, β, δ and θ frequency range. By default, the data items mentioned above, and error messages, are automatically sent to an RS232 port at the rear of the monitor every 5 sec. Software control of this process is possible (a program can stop or re-start the flow of data as required). The data are formatted as ASCII characters, with data elements separated by the "pipe" character ("|").

TCI system

The control actuator of the closed loop system is a propofol TCI system that comprises a Graseby 3400 (Graseby Medical Ltd., Watford, UK) infusion pump, connected to and controlled by a Graseby pump controller (Anaetech Ltd, Leeds, UK). This has been extensively tested and validated, and used in numerous published studies of target-controlled infusions for analgesia, sedation and anaesthesia. Visual and auditory signals warn the user of critical conditions (e.g. mains power interruption, syringe empty, occlusion of drug administration line, no signal received from PC in previous 3 sec).

The pump controller was developed and programmed in-house by Prof. Kenny and Mr. Martyn Gray in collaboration with Graseby Medical Ltd. It can operate in three different modes: manual control (via a dial), computer control via an RS232 port, and

patient-control (via an activating handset). The controller contains pharmacokinetic data sets for numerous hypnotic and analgesic drugs. The dataset for propofol is the Marsh model that is used by the Diprifusor microprocessor (AstraZeneca, Macclesfield, UK).[43] A small LCD screen on the controller displays relevant information such as the target and achieved blood propofol concentrations, and the pump infusion rate. Warning and error messages are also displayed, and supplemented by audible alarms. The maximum target concentration the controller will provide is 15 µg/ml.

SOFTWARE

As our department did not have an in-house computer programmer, I had to write the software. The software program was arbitrarily called BISCLAN (short for BIS-guided closed-loop anaesthesia). A list of the main files associated with the program, and the source code for the main files, are reproduced in the 6 appendices at the end of this thesis. The control algorithm has been published in the "Enhancements" section on the Anesthesiology website (http://www.anesthesiology.org).

Prior to starting the project I had a limited amount of programming experience, having written some simple programs with Turbo Pascal, BASIC and OPL. I believed that an object-orientated programming environment would be best, because it seemed to me to be well-suited to developing a Windows-based user interface, that was flexible and adaptable, and would enable me to re-use units and objects with future applications. I used Borland Delphi version 2 and later version 4 (Inprise Corporation, Scotts Valley, CA, USA) as I was already familiar with the underlying programming language (Pascal), and because I believed that Pascal programming enforces a degree of programming discipline, that would assist an amateur programmer such as myself.

Delphi is a sophisticated object-orientated program development tool. Much of the code is generated automatically, particularly the code for forms and controls which can be chosen from a palette at the click of a mouse button. The properties of these objects (e.g. colour and size) can be set just as easily – very little manual code writing is required to control the size and appearance of a form or control. Nonetheless it was still necessary to write a large amount of code, the bulk of which was concerned with the main program loop, starting up and initialisation routines, and code for events (events are actions associated with objects – e.g. what the program should do if the user clicks the left mouse button over a button on the screen). I had no experience of writing routines for serial port communications, dealing with memory, buffers etc. and the time available to learn these subjects was limited, and so a share-ware serial communications unit was purchased for £10 (TSerial2, later updated to TSerial3, R Crowther, www.getsoftware.com).

The first priority was of course to plan the overall structure of the program. Several parameters that the user had to set before the main program began (e.g. which serial port was being used) were identified, and so I decided to use a separate form and unit to do this. Other parameters (such as the appearance of the interface, or the BIS set point) could, or had to, be set or altered while the program was running, and so the code for these was included in the main program unit. Initially I included all other routines in the main unit, but it soon became very bulky, and so as time went by I made the separate procedures and functions more specific and separated the code for distinct groups of tasks into separate units. As time went on I constantly updated and improved the program. The main program files are as follows:

1. "BISCLAN.dpr": the main project file, generated by Delphi (Appendix 1)
2. "ControlAlg.pas": this file contains the code for the control algorithm (Appendix 2)

3. "BISMainUnit.pas": this is the main program unit. (Appendix 3)

   It contains the code for the controls used on the user interface, for managing data files and for controlling and verifying communications with the TCI system, and of course the main routine (to be described in greater detail below).

4. "BISCLANMainUnit.dfm": this unit controls the appearance of the main user interface.

5. "EEGMonitorControl.pas": code for controlling communication between the PC and BIS monitor (Appendix 4)

6. "StartUnit.pas": this unit is used when the program is started (Appendix 5)

   When it is run it displays a separate form, with controls that enable the user to specify the serial port to be used for communication with the BIS monitor, and to set other program parameters (e.g. whether or not electronic data storage is required)

7. "StartUnit.dfm": unit that controls the appearance of the starting form.

8. "Serial3.pas": this is the shareware serial communications unit – it contains the routines for control of the serial port and memory buffers

9. "TonyExtras.pas": file containing some simple mathematical routines (Appendix 6)

Start-up routine

When the user starts the program, it first runs "StartUnit" and displays a form ("StartForm") (Figure 9.1). The main routines of StartUnit are shown in Figure 9.2.

The chief functions of the start-up form and unit are to verify that the PC is able to communicate with the BIS monitor and TCI system; and to enable the user to set certain important variables (American Society of Anesthesiologists (ASA) status, serial port number for EEG data, data logging required, data logging interval, type of BIS monitor, patient name) and to name and open a data file. Default values are displayed

but the user is able to enter different values (either via text boxes or radio buttons) and once he has clicked on the "Start" button, the program checks the validity of the user-defined parameters. If an invalid value has been entered, or there is a problem with communication between devices, a warning message is displayed and the routine starts at the beginning. Once all the variables have been initialised, and the data file set up and opened, the start-up form is hidden and the main program form is displayed.

Main window and main program loop

The system was designed to run in one of four modes – "monitor only", "manual", "induction" and "maintenance." The latter two modes are automatic modes: in "induction" mode automatic step-wise increases in blood propofol concentration are made until the actual BIS value reaches the set point; whereas in "maintenance" mode the PID control algorithm is used to determine the blood propofol target concentration. Induction mode has not been used clinically, and so the source code for induction mode has been omitted from the control algorithm.

After "StartUnit" has been run the main program form is displayed, the mode is set to "monitor only, " and the main program loop is activated. This loop, summarised in Figure 9.3, calls routines from inside the main unit and from other units, and runs until program shut down is requested – a timer is used to allow a short time gap between successive passes of the loop. With each circuit of the loop the main functions pertaining to the current program mode are performed. Within and after each pass of the loop it is important to allow processing of system messages to enable Windows "housekeeping" functions to continue, and also to allow receipt of any user input (such as a change to the BIS set point). In the latter case operation of a control will result in a piece of "event-related" code for that control. For example if the user wishes to increase

the BIS set point he can click on an upwardly pointing "speed button" and this will cause the value of the set point shown in a text box to be altered and the variable containing the set point to be altered, so that the new set point will be sent to the control algorithm further on in the main loop.

As mentioned above, on start-up, the mode is set to "monitor only." If there is no further user intervention the program performs the data capture and display functions – to start saving data to disk the user has to click on the "Start" button. The program requests the EEG data at the user-specified intervals (default 5 s), displays the BIS and burst suppression ratio, and if required, writes the EEG data to a text file. Event-markers can be activated and chosen from a pop-up menu, or from a page of icons, and are recorded with the following set of EEG data. In this mode the system does not interact with the TCI system, so that any anaesthetic can be used, under the manual control of the anaesthetist.

In "manual" mode, in addition to the data management functions mentioned above, the user is able to control the TCI system via the user interface. The system continuously gets the estimated blood and brain propofol concentration from the TCI system and plots the trend of these values on the BIS graph. It also writes these values to disk with the EEG data.

For "induction" and "maintenance" modes the user is required to enter the BIS set point, and the minimum allowable blood propofol concentration. The system defaults to a maximum blood concentration of 15 $\mu g.ml^{-1}$. In "maintenance" mode the system calculates the difference between the set point and actual BIS values every 5 s, and passes this value to the proportional-integral-derivative (PID) control algorithm, which calculates the propofol concentration required to maintain the actual BIS at the set point.

The majority of the code in the main unit is concerned with controlling the appearance of the user interface, and the code associated with operation of controls. "Screen dumps" of the main program form or window are shown in figures 9.4 and 14.1. Figure 9.4 shows the appearance of the interface just prior to starting to record data in "monitor only mode", whereas Figure 14.1 shows the interface appearance with the system in "manual mode" after a period of time in automatic control ("maintenance mode"). To keep the user interface simple and intuitive, as few controls as possible have been included. Buttons and menus are only visible when active, and can all be operated with either the keyboard or mouse. With future developments in mind, I made the controls large enough to use on a touch-sensitive screen. There are three main screens/windows, each on a separate "tab page".

The main screen (Figure 9.4a) contains the graph of the BIS trend, large digital displays of the latest values of the BIS and burst suppression ratio, the main controls, and small status bars to display the current time and date, and the operating status of the BIS monitor and TCI system. The BIS trend graph is also used to display the blood and effect-site propofol concentration when in "manual" mode (in automatic modes the BIS set point is also displayed). The axes are as follows: left y-axis: BIS, right y-axis: propofol concentration, x-axis: time. For all axes the scale can be changed as required, and for the time axis scrolling backwards and forwards is possible.

The second "tab page" (Figure 9.4b) contains the controls for changing the system mode, and for setting user-defined variables for manual and automatic modes: for manual mode the desired blood propofol concentration and for automatic mode the BIS set point and the minimum allowable propofol concentration. The third tab page has icons that can be used for recording event markers (e.g. "start of induction", "loss of

consciousness" and "incision") along with the EEG data. A pop-up menu of text descriptions of events can be accessed with a right mouse click over this window.

PROGRAM DEVELOPMENT, DEBUGGING AND TESTING

The code for the interface was written first. After that the main program loop was designed and written, and then, in order, the code for "monitor only", "manual", "induction" and "maintenance" modes were written. Testing and debugging was done once the code for each of the modes was completed.

"Monitor only" mode

The software for "monitor only" mode proved to be the most difficult and time-consuming to write and debug. To simplify the programming task, the program flow was designed to run in a linear manner, but the disadvantage of this is that a delay at any stage has the potential to interrupt the whole program flow. Display and storage of the data was fairly simple. The difficulties were related to the routines for controlling communication with the BIS monitor, specifically the routines for retrieving the data from the memory buffers.

The shareware serial communications unit, "TSerial3", can be set to receive data character-by-character or as whole strings. Whole strings are generally easier to deal with, but TSerial3 unit can only cope with incoming string lengths of up to 256 characters, whereas each EEG data string from the A-1000 BIS monitor is longer than that (most of the relevant EEG data is within the first 256 characters). Also, data string sent to the serial port arrives in the buffer in separate packets, so that if TSerial is instructed to read the memory until the buffer is empty, it often returns incomplete strings, and subsequent strings may contain over-lapping data bits.

The solution used was to use control the data output from the monitor (the default is for automatic updates every 5 sec). It is not possible to request a single data string – one can only switch the data flow ("updates") on or off. Thus the solution was to switches the updates on when data are required, wait for and receive the first string, and then immediately switch off the updates. The serial port component is used to retrieve the whole string by reading the buffers one character at a time and then to re-build the strings again in the main program unit. With this method it is important to be able to identify the ends of the strings. I struggled for weeks, without success, to identify the ends of the strings using the apparent number of characters in the strings. The problem and solution, identified by chance, is that the ends of the strings are marked by the null character (not mentioned in the product manuals)!

"Manual" mode

The next main step was to write and test the extra code required for "manual" mode – the routines for controlling the TCI system. To control the TCI system the PC has to send a data string containing the target propofol concentration (as an integer representing concentration in µg/dl), preceded and followed by control characters. After receiving an instruction the TCI system replies with a string containing the current estimated blood and brain propofol concentration. This makes it easy to verify that an instruction was received and that communication is secure. When controlled by an external computer, the TCI system must receive regular instructions (at least once every 30sec), otherwise it assumes communication has been lost and emits an audible alarm.

For sending and receiving these data, simple integer-to-string and string-to-integer routines respectively were required, with routines to check that the target concentrations were within safe limits. Other simple routines were required to set

variables to indicate communication status, display this status information on the status bars and to store and display the current blood and brain propofol concentrations.

The interface was designed to allow the user to control the TCI system (in "manual" mode) by clicking on up or down "speed buttons" or by typing the target propofol concentration (in ng/ml) in a text box. Once the text box has been altered or a speed button activated, an event trigger runs a routine to convert the value entered to an integer (representing concentration in μg/dl) and to set the target propofol variable. This value is then sent to the TCI system during the subsequent pass of the main loop.

As mentioned earlier, when controlled by a PC the TCI will alarm if regular communication strings are not received. If communication between PC and TCI system is interrupted then the TCI system continues with the current target propofol concentration, and can be controlled manually (by means of a dial/wheel).

Thus, testing of the software for "manual" mode was fairly simple – all that was required was to test that the propofol concentration set by the user was correctly transmitted, and that returned values were correctly interpreted, stored and displayed; and that if there was a problem with communications (i.e. no reply or invalid reply from TCI system), then appropriate messages were displayed on the status bars and the main body of the screen is changed to red if two successive communication attempts fail. These routines were tested separately by copying them into a simple test program, containing a similar user interface, but with "monitor only" functions removed or inactivated, and then testing them within the main program. The TCI system was loaded with an empty test syringe, and a broad range of concentration values (beyond those allowed) likely to be used were sent to it. The response and behaviour under critical events such as occlusion if the intravenous drug administration catheter, and

disconnection of mains power supply or the serial communication cable, were also tested.

"Maintenance" mode

In this mode a control algorithm determines the target propofol concentration every 30 sec. The control algorithm was the same as that used by an AEP-guided closed loop system developed in Glasgow by Mantzaridis.[121] The advice received was to use the identical control parameters. During the first clinical study of closed loop control with this system problems with oscillation were encountered. I thus later made the decision to alter the gain parameters in an attempt to damp the response of the system.

To simplify programming the control algorithm was run by a separate unit ("ControlAlg.pas") that was adapted for Delphi and the BIS from that used in the AEP system. During each pass of the main program loop (± every 5 sec) the current values of the BIS and blood propofol concentrations are sent to the control algorithm. Based on those values the algorithm determines and stores an interim adjustment value (called DeltaTrgtProp). The interim values calculated during each 30 sec interval are summed to generate a variable called SumDeltaTrgtProp, and at the end of each 30 sec interval the algorithm checks that it is less than a set limit (dependent on ASA status) – if it is greater than the limit then the limit value is used. The algorithm then adds it to the current blood propofol concentration, and returns the greater of that value and the minimum allowed propofol concentration to the main program, where the target propofol variable is updated and used during the following pass of the main loop.

Testing of the software required for "maintenance" mode was done as follows. To check that the control algorithm was implementing correctly, the monitor functions were disabled, and the main loop altered to read experimental BIS data from a text file.

The text files contained sequences of BIS values that changed in various simple ways: no change, gradual step-wise increases and decreases, and large single step-wise changes, followed by stable values. The output from the algorithm was recorded and compared with that determined by manual calculations and also from the output of Excel spreadsheets programmed with the control algorithm.

The penultimate step was to test the system with "live" BIS data from patients undergoing general anaesthesia, but with anaesthesia induced and maintained by a propofol infusion controlled by an anaesthetist. The TCI system that was part of the closed loop system was loaded with a dummy syringe not connected to the patient. Another anaesthetist checked that the magnitude and direction of the changes were consistent with clinical practise. The BIS values and the target propofol concentrations calculated by the program were recorded for later verification that the algorithm was being corrected implemented. These tests also gave a broad indication of the expected response of the system to changes in the BIS and to the set point. The data from one such trial are shown in Figure 9.5.

The control algorithm had performed satisfactorily when implemented and used in large numbers of patients in whom anaesthesia was controlled by the AEP-based system. Once it was clear that it had been correctly implemented by the new BIS-guided system formal clinical trials of the performance of the system in patients were begun. Three such studies were performed and will be discussed in chapters 15, 17 and 18.

DISCUSSION

This project was pivotal to my work in Glasgow, because the system was required for all the subsequent studies. It was a difficult and time-consuming task, particularly for an amateur programmer, but the end result was a system that is easy to use, works well and

because of the modular nature of the software, can easily be adapted for use with other control variables.

The advantages of the system are that I developed it myself, so that I understand it, and don't have to rely on assistance from others with program maintenance or debugging. A weakness of the system is that it uses control parameters tuned for an AEP system. Although the AEP has a roughly similar scale to the BIS, it does not respond in an identical way to changing conditions (be they changes in surgical stimulus, or in drug concentrations). Also, as will be discussed in a chapter 15, the classical PID control algorithm may not be the best algorithm for clinical use. Nonetheless, as will be seen in chapters 13, 14 and 19, the system performed remarkably well when tested clinically.

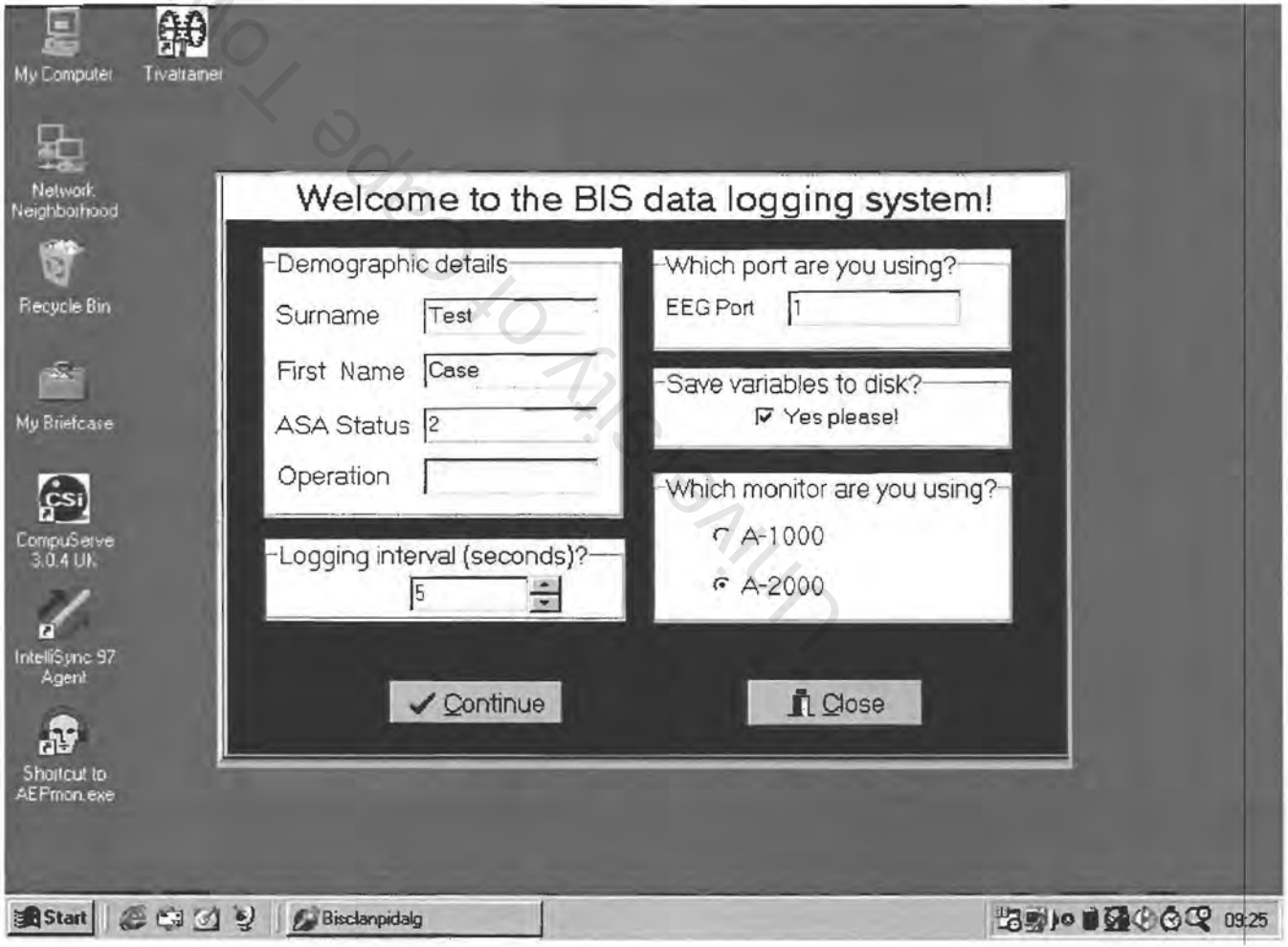


Figure 9.1: Screen dump of "StartForm" which is the first form displayed when the program is run

Figure 9.2: Schematic of main events in start-up routine

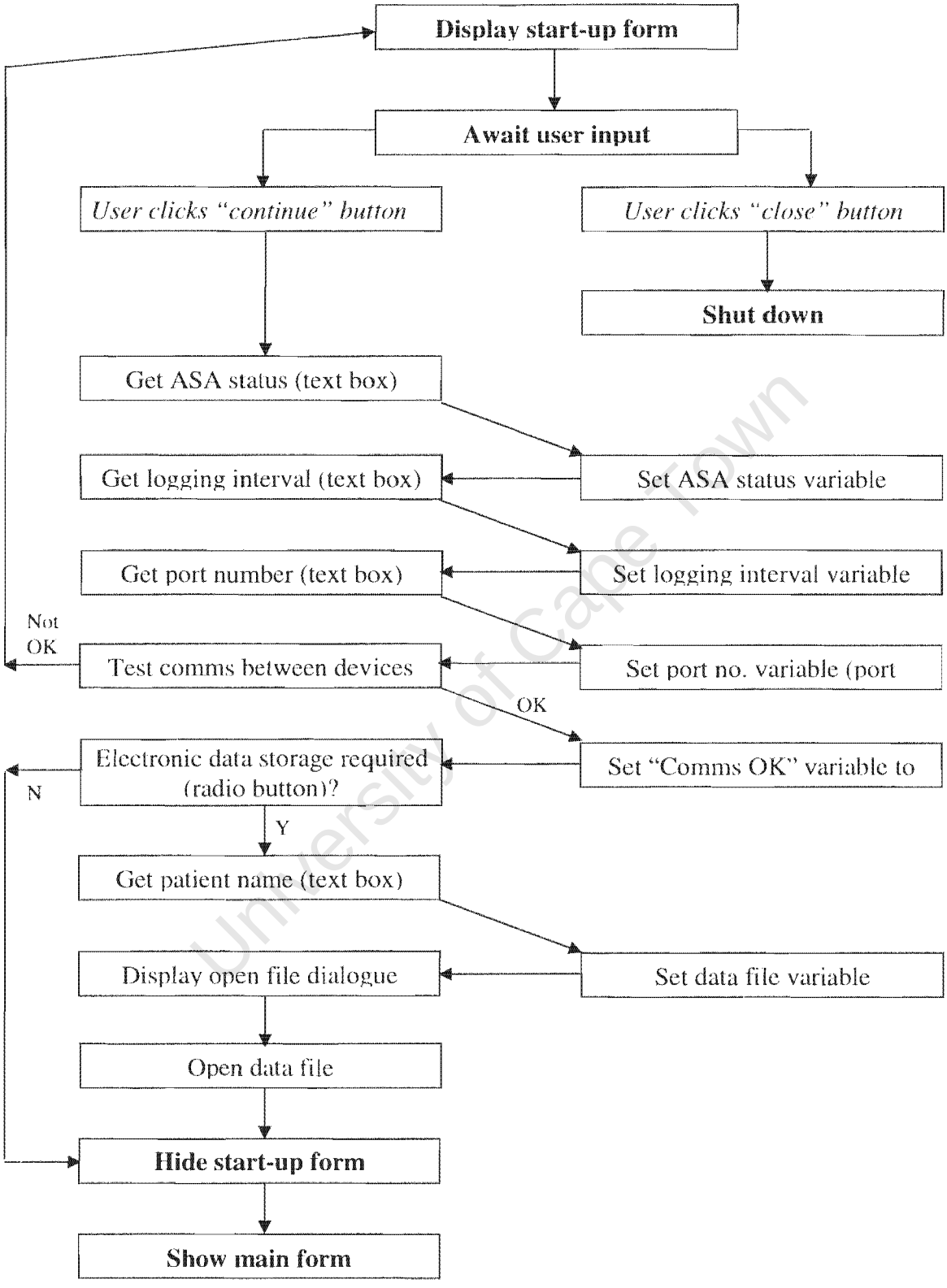
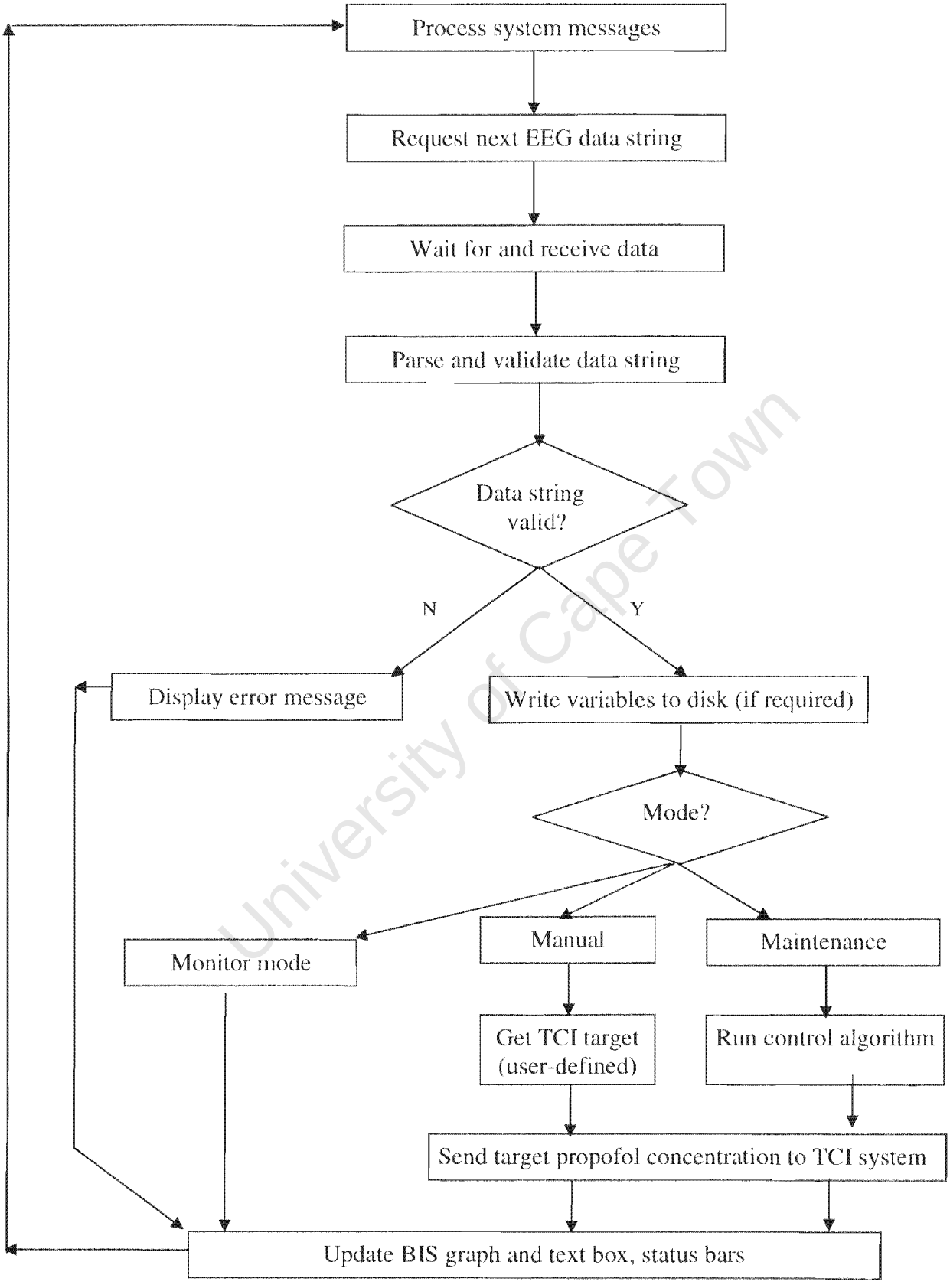


Figure 9.3: Schematic of main program loop



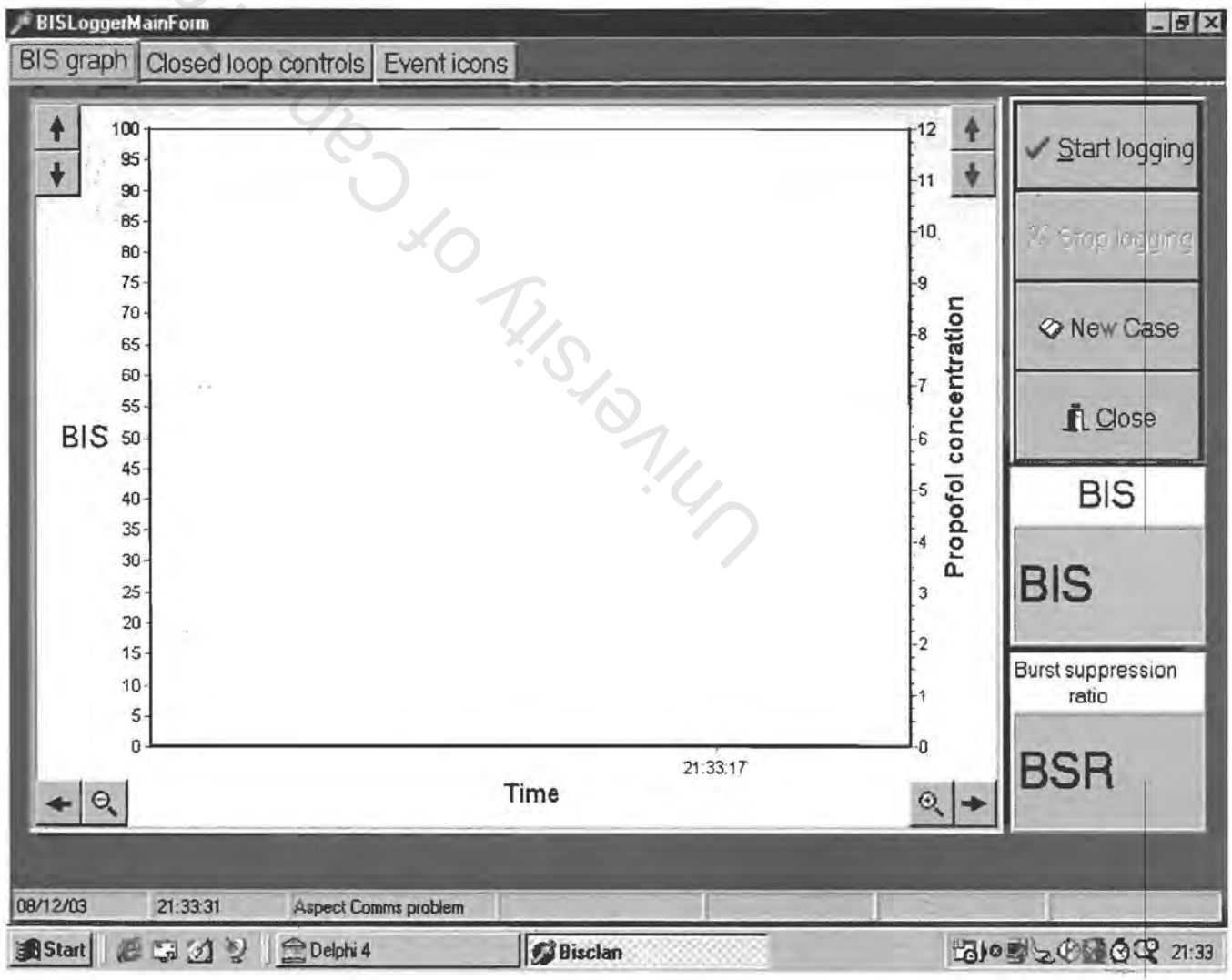


Figure 9.4a: Front "tab page" of main program unit form – the status bar is indicating a communication problem with the BIS monitor

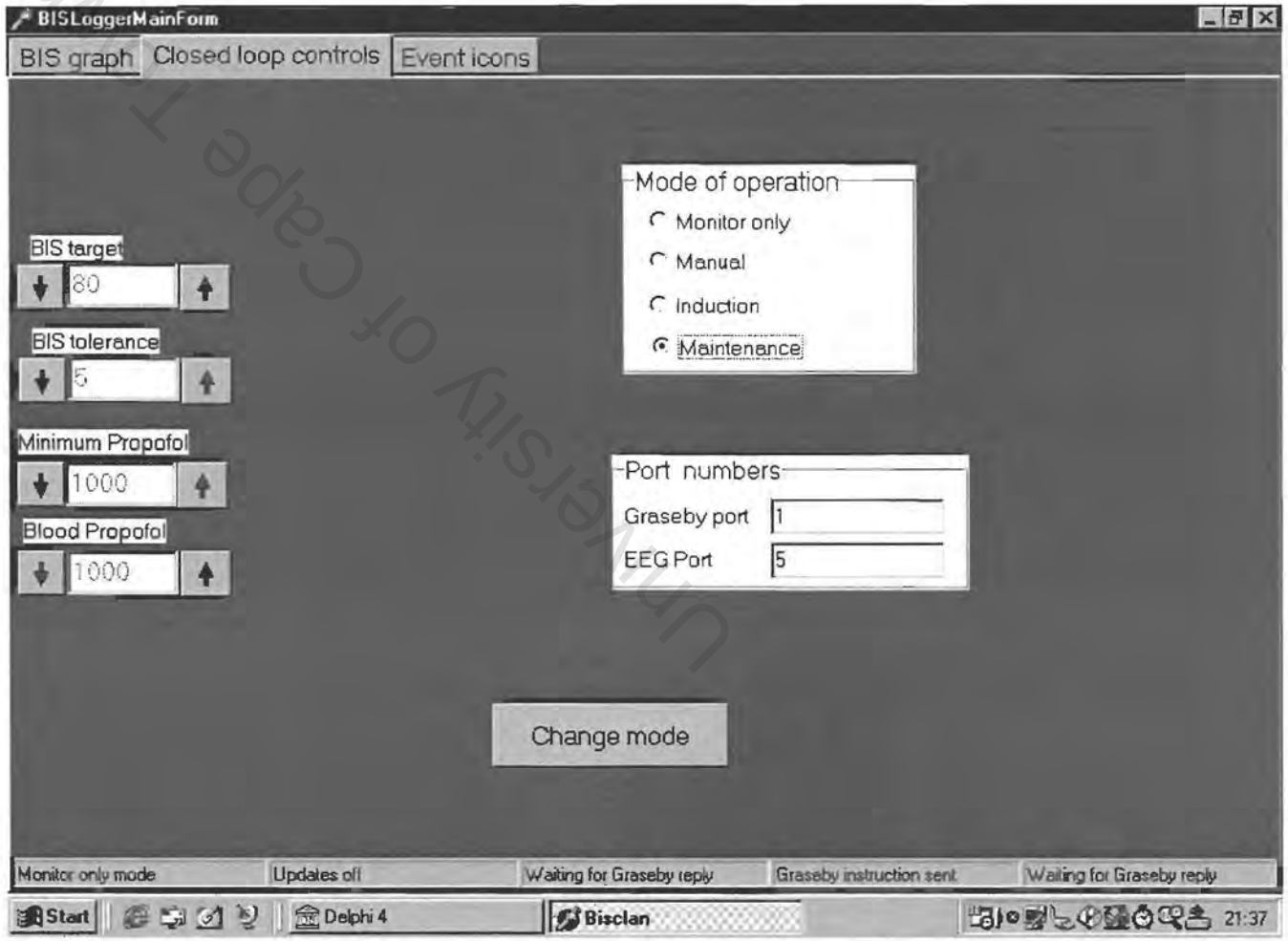
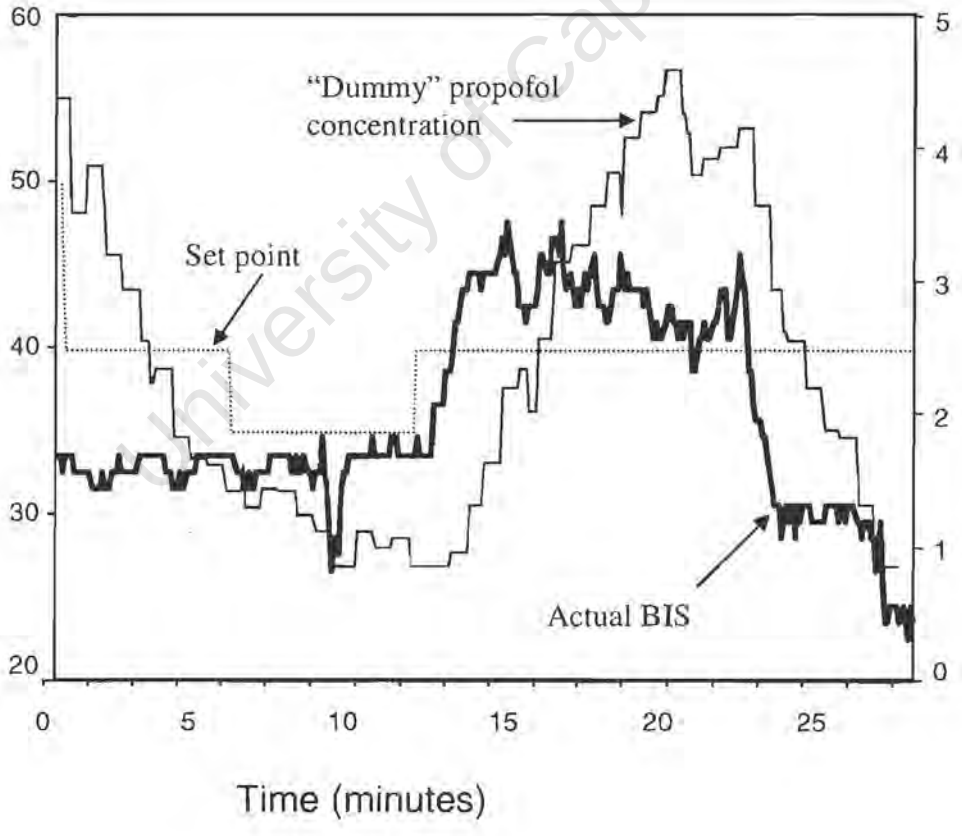


Figure 9.4b: Second "tab page" of main program unit form, containing controls for changing mode and those for use in manual and automatic modes (currently a dull colour to indicate that they are inactive). A change mode request has just been made (to change from monitor only to maintenance mode), and the program is busy verifying communication status with the Graseby TCI system

Figure 9.5: Data from a test of the closed loop program, where live data from a patient undergoing general anaesthesia using a propofol infusion. The closed loop system was set up as if for use on the patient except that the TCI device was loaded with a dummy syringe not connected to the patient. Anaesthesia was provided by a separate TCI propofol system controlled by another anaesthetist (target concentration was 4.5 μg/ml during the test period). During maintenance of anaesthesia the virtual target propofol concentration was set to 4.5 μg/ml and the closed loop system was switched to "maintenance" mode. The virtual BIS set point was altered as shown by the dotted line, and the program output (target propofol concentrations) by the light continuous line. The heavy continuous line depicts the actual BIS values. For the purposes of the test it was assumed that a change to the target propofol concentration resulted in an instantaneous identical change to the blood propofol concentration. The stored data were later analysed to verify that the algorithm had been correctly implemented.



The Bispectral Index

Chapter 10

Bispectral analysis and the Bispectral Index: description, literature overview

Frequency domain analyses of the EEG suffer from several limitations. As anaesthesia deepens the frequency spectrum undergoes changes that are only obvious to the trained observer. To simplify matters the spectrum is sometimes summarised with univariate parameters such as the median or spectral edge frequency, but these parameters do not vary monotonically with depth of anaesthesia – during induction of anaesthesia the median frequency may first rise before it falls, so that one value may be associated with two entirely different clinical states in one patient. Part of the reason for this problem is that the brain is not a linear system – typically not all frequency components are independent – and frequency domain methods are unable to differentiate between faster components that are independent waves (i.e. arising from neural elements acting at higher frequencies) and components that are harmonics of slower waves.

Bispectral analysis is a higher order signal processing technique that uses both frequency and phase analysis. It assesses the phase relationships or bicoherence among component frequencies and is able to determine whether or not higher frequency components are likely to be harmonics. The process involves determining the bicoherence among all possible triplets of frequencies contained in the spectrum, where the frequency of the fastest component is the sum of the frequencies of the two slower components of the triplet.

This process is summarised in Figure 10.1, which illustrates how two different waveforms can have identical frequency spectra (both waves have 2 Hz, 3 Hz and 5 Hz

components of similar power at each frequency). The difference in the appearance of the time domain representations of the two waves is because of phase differences among the component frequencies making up the signals. These are revealed by bispectral analysis, which demonstrates a phase relationship between the 2, 3 and 5 Hz waves in the left-hand waveform, but none in the right-hand waveform.

Geophysicists were the first to introduce and use bispectral analysis when they used it to study various natural phenomena in the early 1960s.[122] It was first applied to EEG analysis in the early 1970's, [123] but further development was only possible in later decades with improvements in computing power. During the surgical planes of anaesthesia, increasing depth of anaesthesia is associated with synchronisation and increasing phase coherence among component frequencies – there are fewer neural generators, and higher frequency components are more likely to be harmonics than independent waves.

In the late 1980's and early 1990's Aspect Medical Systems developed a depth of anaesthesia monitor that used a combination of time domain, frequency domain and bispectral analysis of the spontaneous surface EEG to derive an index of anaesthetic depth (the Bispectral Index or BIS). During the development of these monitors EEG data were recorded from a large number of patients undergoing general anaesthesia. Discriminant analysis was then used to determine which of a large number of parameters calculated offline were best at predicting the depth of anaesthesia (as determined by the clinical judgement of anaesthetists). Through this process it was determined that the most useful parameters were the burst suppression ratio (or BSR, derived by time domain analysis), the "BetaRatio" (derived by frequency analysis), and "SynchFastSlow" (derived by bispectral analysis). Each parameter provides varyingly useful information at different depths of anaesthesia. The BetaRatio is useful during

light sedation, whereas the BSR is most useful during very deep anaesthesia and SynchFastSlow is most useful during the stages between moderate sedation and surgical anaesthesia.

The BIS is the weighted sum of these sub-parameters. These weightings are determined dynamically by pattern recognition algorithms – thus if the EEG shows a burst suppression pattern, then the higher order parameters are largely ignored. The exact BIS algorithm is proprietary, secret information, and has been refined and updated many times over the past decade, as the size of the patient database has increased and also as newer information has come to light.

Initially the BIS was designed to predict response to surgical stimuli. Retrospective analysis of the EEG data from the patient data base suggested that the BIS correlated well with haemodynamic responses to intubation [124] and with the likelihood of movement in response to surgical stimuli.[125-127] Later a large prospective trial of the real-time utility of the BIS confirmed that the BIS is a significant predictor of movement response to incision for hypnotic-based techniques, but not for opioid-containing techniques. [128] At this stage there was already mounting evidence (from animal work) that movement responses during anaesthesia were related to spinal reflexes and were thus related to analgesia rather than to hypnosis.[11;129;130] Several later studies confirmed the inability of the BIS to predict movement responses to noxious stimuli. [99;129-132]

The emphasis then shifted toward proving the correlation between the BIS and other measures or indeces of depth of sedation and anaesthesia. Liu and colleagues showed that the BIS was better able to predict the depth of midazolam-induced sedation (as judged by the OAA/S scoring system) than the SEF and MF.[133] Glass and colleagues then showed that the BIS correlated very well with the level of sedation induced by

propofol, isoflurane and midazolam, and was a better predictor of level of sedation and of loss of consciousness than the measured arterial drug concentration.[134] Struys and colleagues showed that the BIS correlated well with depth of propofol induced anaesthesia, whereas SEF, MF, frontal spontaneous electromyography and relative delta power did not.[93] Later, when comparing the BIS and the AEPindex, Kurita and colleagues showed that both measures had high prediction probabilities for the depth of sevoflurane-induced sedation, but that after loss of consciousness the BIS was not as efficient as the AEPindex and the end-tidal sevoflurane concentration at predicting movement on insertion of a laryngeal mask airway.[131]

More recent studies have shown that in patients undergoing general anaesthesia the BIS compares favourably with SEF, approximate entropy and changes in heart rate variability.[75;82;83] A study by Struys of patients undergoing induction of anaesthesia, found that the BIS compared favourably with the predicted effect-site propofol concentration and the AAI, in terms of prediction probability for level of sedation and loss of consciousness.[99]

Other studies showed that the BIS also correlates very well with measured [135] and predicted [136] blood propofol concentrations and that BIS monitoring can reduce anaesthetic drug usage and costs,[137-140] reduce recovery and discharge times and costs, [137;139;141;142] and improve the quality of post-operative recovery. Most importantly it has recently been shown that among patients at high risk of inadvertent awareness BIS monitoring reduces the incidence of awareness. [57]

SIGNAL ACQUISITION AND ANALYSIS

Most of the information concerning the BIS computation algorithm that is in the public domain is provided in two technical papers on bispectral analysis and EEG processing written by Sigl [122] and Rampil.[143]

EEG signals are detected by electrodes applied to the scalp. Common mode amplification is performed by an amplifier contained in a separate box close to the patient, to reduce the amount of noise interference. After amplification the signals are sent to the main monitor where low and high pass filtering are applied (to remove frequency content/artefact >70 Hz and <0.5 Hz respectively). Mains frequency notch filters are also applied. The signal is then digitised at 128 Hz before being divided into 2 sec epochs. Further artefact filtering algorithms are applied to the epochs to exclude, for example, artefact caused by the ECG, pacer spikes and eye blinks – where possible the data are "repaired", otherwise contaminated epochs are excluded from analysis. Finally the amplitude variances of successive epochs are compared. Epochs with variance much greater than previous epochs are also excluded. The remaining data are then subjected to further analysis.

Two time domain methods are used to determine the degree of burst suppression. The Burst Suppression Ratio represents the proportion of the previous 60 sec during which there was electric silence, where silence is defined as a period of >0.5 sec during which the voltage is < 5mV. In the presence of a wandering baseline (i.e. low frequency components) this definition of electrical silence may cause some burst suppression to go undetected. Thus, QUAZI, an algorithm incorporating slow wave information (<1 Hz) is also used.

The remaining sub-parameters are calculated from frequency domain and bispectral analysis. First, a mathematical "windowing" technique, such as a Blackman window, is applied to reduce the distortion in the results of frequency analysis that

would otherwise be generated by epoch end (and start) artefacts. [143] The "window" is a matrix of numbers calculated from a formula. The number of elements in the matrix is the same as the number of samples in the data epoch, and each item in the data epoch is multiplied by the corresponding element in the window matrix. A Blackman window applies a bell-shaped alteration to the signal amplitudes in the epoch – towards the start and end of the epoch the amplitude of the signal is gradually reduced to zero, whereas in the centre of the epoch the original amplitudes of the samples are retained. Fast Fourier Transformation (FFT) is then performed. This yields a series of complex numbers, each comprising a real and an imaginary component, and each associated with a frequency that is a whole number multiple of the fundamental. From these complex numbers the power and phase of each frequency component in the signal can be calculated.

Frequency domain analysis is used to calculate the "BetaRatio", the log ratio of power in two frequency bands: 30 – 47 and 11 – 20 Hz. Bispectral analysis, which uses both power and phase information, is used to calculate "SynchFastSlow", calculated as the log ratio of the sum of bicoherence between two frequency bands: 0.5 – 47 Hz and 40 – 47 Hz.

Earlier versions of the monitors used up to 60 sec of data to calculate the BIS. This processing delay has now been reduced, and the newer monitors can calculate the BIS from as little as 15 sec of artefact-free data. The user of the monitor has the choice of selecting a smoothing interval of either 15 or 30 sec.

DATA OUTPUT

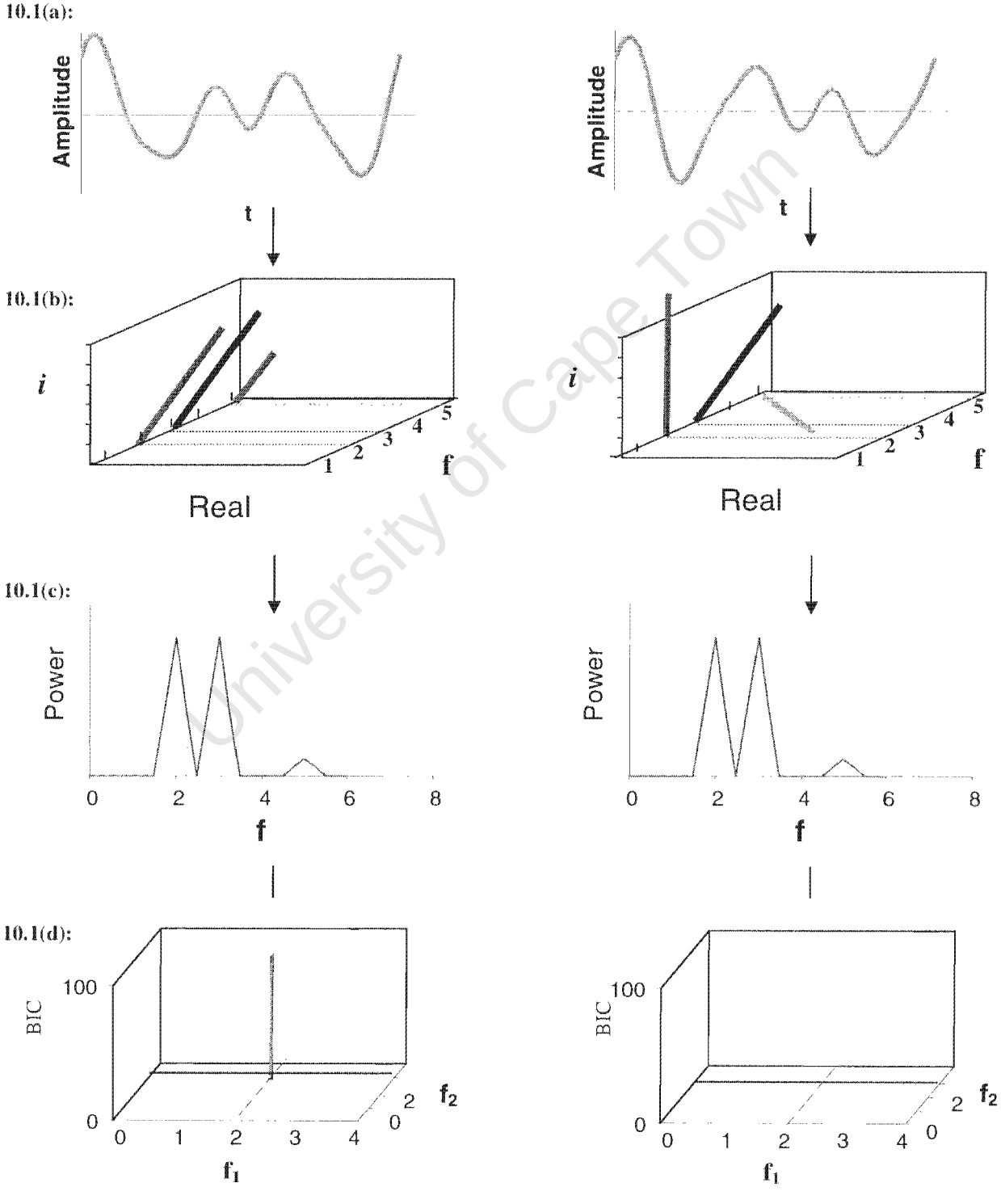
During the studies that underpin this thesis two BIS monitors were used: initially the A-1000, and later the A-2000. The A-1000 monitor calculates four channels of data from two pairs of electrodes in positions AT1 and FP1, AT2 and FP2, with a ground

electrode at FPZ. BIS values displayed on the monitor screen are the averages of the left and right channels. Original versions of the A-2000 monitor were designed to be able to calculate two channels of data, using a strip containing electrodes in positions AT2 (or AT1), FP2 and FPZ (ground). However, the BIS values displayed on the monitor screen are those calculated from one channel with AT2 the active and FP2 the reference electrode. A newer BIS monitor, the A-2000 XP™, uses a strip of four electrodes, but was not used in any of my studies.

The monitor screen displays the current BIS and burst suppression ratio (BSR), the BIS trend over time, the signal quality index (SQI) and an index of EMG power. It is also possible with both monitors to display a secondary trend such as EMG power or SEF, or even to display the density spectral array.

Every 5 sec a string of data is assembled and sent to the RS232 port – as mentioned before this process can be subjected to software control. The string starts with the date and time, followed by the filter settings, error and alarm codes, SQI and EEG data for each channel – the A-2000 monitor calculates and outputs the BIS (as calculated from the current and previous software version), the SEF, BSR, total EEG power and EMG power. The A-1000 monitor also calculates and outputs the median frequency and the absolute and relative power in each of the traditional EEG frequency bandwidths. Data items are separated by the "pipe" character.

Figure 10.1: Frequency vs. bispectral analysis. Time domain representations of two different signals are shown in Fig. 10.1(a). Fig. 10.1(b) shows the results of FFT: the complex numbers associated with each frequency are plotted as vectors in parallel 2-D planes. Frequency analysis (Figure 10.1(c)) shows that each waveform contains a 2, 3 and 5 Hz component of similar power. Bispectral analysis (Fig. 10.1(d)) indicates that in the left hand waveform the 5 Hz component may be a harmonic of the 2 and 3 Hz components, whereas in the right hand waveform the frequencies are unrelated.



Chapter 11

Project 2: **Correlation between BIS and clinical endpoints**

BACKGROUND

During the planning phase for the studies of this thesis (early in 1998) the body of literature supporting the BIS was much smaller than it is now, and many of the frequently quoted papers involved small numbers of patients or subjects.

The monitor manufacturer was, and still is, recommending a BIS of 40 – 60 during surgical anaesthesia. However, the data contained in the database used by Aspect Medical Systems Inc. to produce the BIS algorithm are not in the public domain. A study, performed in Glasgow, in which the BIS was compared with other parameters (such as the AEP) in 12 patients had shown a large variation in the BIS values at which patients lost consciousness, and also in the values at which consciousness was regained.[92] More importantly, there was overlap between BIS values found during the conscious and unconscious states.

During the planning stages of the BISCLAN system I realised that a database of BIS values during surgical anaesthesia was required, to enable a rational choice of set point during closed loop control. The primary aim of this study was thus to record the BIS in as many patients as possible, before and during a variety of operations performed under a variety of anaesthetic techniques, and to quantify the BIS found at clinical stages or events. This study also provided the opportunity to explore the issues of memory before, during and after anaesthesia, incidence of nausea and vomiting, and patient satisfaction after BIS monitored general anaesthesia.

METHODS

BIS data

BIS data were collected from 200 patients undergoing BIS-monitored general anaesthesia. Of these 200 patients, 50 were involved in one of 3 clinical studies (discussed in chapters 12, 13 and 14) during which anaesthesia was either computer-controlled, or manually controlled according to a strict protocol using BISCLAN, and during which the BIS data were stored automatically on a computer hard disk as part of the study. For these patients written informed consent was obtained.

The remaining 150 patients were undergoing general anaesthesia for a variety of surgical procedures (ranging from minor body surface surgery, to major joint replacements and laparotomies), with the anaesthetic doses administered according to clinical judgement, based on experience and clinical signs. In this operating theatre we routinely monitored and recorded either or both of the BIS and AEP, and routinely visited the patients during the postoperative period to ask them questions relating to memory and patient satisfaction. Anxious patients received temazepam pre-medication 1 – 2 hours before their operation (adult males received 30mg, adult females 20mg).

The anaesthetist (myself) was not blinded to the BIS values. However, the aim was to control the anaesthetic according to clinical signs of anaesthetic depth, and not the BIS. For these 150 patients informal (verbal) consent for application of the BIS electrodes was sought. The data collected were regarded as routine physiological data, and thus any analysis as secondary analysis of routine data, and so neither ethics committee approval nor formal consent was obtained. No patient identifiable data items were kept together with clinical or physiological data. Clinical and physiological data were stored with an index number, the key to which was kept in a secure file (see "Demographic data" below).

The following data were collected:

1. "Demographic data"

   Patient-identifiable data such as name and hospital folder number were stored in a secure separate file, in which each patient was assigned an index number. Relevant history or co-morbidities were also recorded. This information was an abbreviated subset of the data that anaesthetists in Britain were routinely required (by the Royal College of Anaesthetists) to record for all patients under their care, in a database using software provided by the College. All the clinical and physiological data that were stored, and studied, were securely separated from any patient identifiable data.

2. Surgical and anaesthetic details

   Nature of the operation, dose and mode of administration of anaesthetic drugs (including premedicants and muscle relaxants), and the mode of ventilation were stored in a database, with the index number for each patient mentioned above.

3. BIS data

   For 51 patients BIS data were recorded manually (pen and paper) and later copied into an Excel spreadsheet – data recorded were the initial BIS value and then the BIS at the time of the following clinical events: loss of consciousness (loss of eyelash reflex), 30 sec after loss of consciousness, start of tracheal intubation or laryngeal mask insertion, start of surgery, patient movement (spontaneous or in response to noxious stimuli), end of surgery, response to voice, eye opening, and when the patient was able to state their date of birth.

   For the 149 patients in whom the BIS data were recorded electronically, the data strings produced by the BIS monitor were captured and stored in a text file, as described in chapter 9. Each data string contains the date and time followed by the

monitor settings, error messages and EEG variables (including SEF, BIS and EMG power). These data were recorded throughout the anaesthetic from before induction of anaesthesia until the patient was able to state their date of birth. When the clinical events mentioned above occurred, a standard description (chosen from a pop-up menu) was inserted into the next data string. When anaesthesia was either controlled automatically by the computer, or manually via the PC, the target and estimated blood propofol concentrations were also appended to the data strings. The text files were later imported into Excel spreadsheets. Lookup functions were used to extract the BIS values found at the clinical events, and these were stored in the summary spreadsheet also containing the manually recorded data.

Memory and satisfaction data

All patients were visited post-operatively. When it was possible and practical to visit the patient more than 2 hours after the end of their anaesthetic, they were asked the standard questions shown below. The purpose of the questions were first explained, along with an explanation that the data would be stored and analysed. Where verbal consent for this was granted, the answers to the questions were recorded.

1. What is the last thing you remember before you went to sleep?
2. Where did you awake? THEATRE / RECOVERY / WARD
3. What is the first thing you remember after waking up?
4. Do you remember any dreams or noises from during your anaesthetic? YES / NO
5. Would you be happy to have the same anaesthetic again? YES / NO
6. Have you had a previous anaesthetic? YES / NO
7. Compared with the last was this one… SAME / BETTER / WORSE

8. Have you felt sick or vomited since the anaesthetic? NAUSEA / VOMITING / NONE
9. Any other comments?

Patients who reported dreams or noises, were asked for further details such as what they heard or whether they thought they had had the dream or heard the noises during or after their operation.

These data were collected from 109 patients, stored manually on paper and later transcribed into a Microsoft Access database for further analysis.

Statistical analysis

Statistical analyses were performed with the aid of SPSS software (SPSS Inc, Chicago, USA). BIS data at the different clinical endpoints were tested for normality. BIS values prior to administration of any anaesthetic agents, and the BIS values recorded when the patients were able to state their date of birth, showed a moderately large negative skew (skewness values for the BIS values during the two states were –1.94 and –0.85 respectively). BIS data recorded at all other clinical events was approximately normally distributed. Thus BIS data at the different endpoints is summarised using non-parametric methods. The memory and satisfaction data were summarised but were not tested for statistical significance.

RESULTS

BIS data at clinical events

Two of the patients had anaesthesia induced and maintained with volatile anaesthetic agents – one with enflurane and the other with sevoflurane. Twenty-seven patients had

an intravenous induction followed by inhalational maintenance of anaesthesia (isoflurane or sevoflurane), whereas 171 underwent total intravenous anaesthesia.

The BIS values found at different clinical events are summarised in Figure 11.1. The BIS values found before induction of anaesthesia fall into a narrow range – all were between 84 and 98. At all other points there is wide variation in the values encountered. Nonetheless, with the exception of the BIS values found at loss of the eyelash reflex, there is good separation between the awake BIS values recorded before the start of the anaesthetic and those recorded during periods of unconsciousness – in fact, with the exception of 3 outliers (statistically defined as a data point that lies between 1.5 and 3 multiples of the interquartile range above the top of, or below the bottom of, the interquartile range), the full ranges do not overlap. There is however considerable overlap between the values found during surgical anaesthesia and those found when consciousness returns – thus in the range 55 to 80 the sensitivity and specificity for unconsciousness are poor. Patients that moved during surgery tended to only do so when the BIS was greater than 70, although there was one patient who moved when the BIS was close to 40. It is quite likely that this movement was mediated by spinal reflexes rather than involving cortical processing.

Figures 11.2 and 11.3 are typical examples of the trends in the BIS and SEF recorded from patients undergoing short surgical procedures under general anaesthesia (time of occurrence of clinical "marker" events is also shown). The patients from whom the data in the figures were recorded were undergoing sigmoidoscopies. Both were fit, young adults in whom anaesthesia was induced rapidly – with propofol and remifentanil in the first patient (Figure 11.2) and with propofol and fentanyl in the second patient (Figure 11.3). Anaesthesia was maintained with intravenous infusions of propofol and

remifentanil in the first case, and by inhalation of isoflurane and nitrous oxide in the second.

Memory and satisfaction data

Memory and satisfaction data from 110 patients were recorded.

Awareness, dreams or noises

No patient had any spontaneous recall of intra-operative events or noises. Six patients reported dreams – one dreamt about a park, one dreamt about her son, one about the supermarket, one couldn't remember the dream, and the remaining two patients did not volunteer the content of their dreams. Three of the 6 patients reported that the dream had happened in the recovery room. The remaining 3 patients were not sure when or where they had had the dream. None felt disturbed or traumatised by their dream.

Last memory before loss of consciousness

This question was added to the questionnaire partway through the study. Thus only 38 responses were received. Most patients questioned had remarkably clear memories of events immediately prior to losing consciousness. Five (13%) reported that their last memory was of pain in the arm (secondary to propofol injection). Many others were able to recall the content of conversations that were happening while they lost consciousness, several remembered seeing a clock on the wall and one correctly remembered the exact time that the anaesthetic was started.

First memories after return of consciousness

All patients were kept in the operating theatre until they had regained consciousness, and if practical, until they had stated their date of birth. They then spent at least 20 minutes in the recovery room before being returned to their ward. As part of the questionnaire they were asked where they thought they had regained consciousness, indicating the point in time when their working memory function returned. These data are summarised in Table 11.1. Of the 110 patients questioned post-operatively only 14 (13%) recalled regaining consciousness in the operating theatre, whereas 85 (78%) thought they had "woken up" in the recovery room, and 10 (9%) thought they done so on the ward. One patient was unsure where was when she woke up. Those patients who thought they had regained consciousness in the theatre had similar final BIS values (when they stated their date of birth) to those who thought they had regained consciousness in the recovery room or the ward.

The presence or absence of pain did not influence where the patients were when their memory function returned. None of the patients who correctly believed that they had regained consciousness in the operating theatre, and none of those who thought they had woken up on the ward, reported pain as their first memory. Of the patients who thought that they had woken up in recovery, 9 reported pain and 1 a sore throat as their first memory. Neither temazepam pre-medication nor the method of maintenance of anaesthesia (inhalational versus intravenous) influenced where the patient believed they had regained consciousness. Patients undergoing total intravenous anaesthesia tended to have infusions of propofol and remifentanil; whereas patients undergoing inhalational anaesthesia received either isoflurane or sevoflurane supplemented with intravenous bolus doses of alfentanil or fentanyl.

Patients' first memories during the post-operative period were usually concerned with the staff looking after them.

Post-operative nausea and vomiting (PONV)

Of the 86 patients in whom TIVA was used, 82 (95%) had no PONV, 4 (5%) suffered from nausea, and none vomited. The 4 patients who suffered from nausea had had a previous general anaesthetic; and 3 of them rated their anaesthetic as better than their previous anaesthetic. Of the 24 patients to whom volatile anaesthetic agents were administered for maintenance of anaesthesia, 18 (75%) had no PONV, 5 (21%) suffered from nausea, and 1 (4%) suffered from vomiting.

DISCUSSION

A broad range of BIS values are found in different patients during supposedly similar clinical states. Methods used to assess the ability of the BIS to predict whether or not a patient will be awake or unconscious at different values include preparation of receiver-operator curves, and calculation of Pk values.[144;145] The latter technique has been used in several studies comparing the prediction ability of the BIS with other parameters such as blood propofol concentrations, and other EEG-based measures of anaesthetic depth.[146-149] A full discussion of these techniques and their application to the current data are beyond the scope of this thesis. Despite the broad inter-individual variation, the BIS trend in an individual patient appears to be significant

There are many factors that may contribute to the inter-individual variation in the BIS found in this and other studies. Firstly, as discussed previously, clinical signs are surrogate markers of anaesthetic depth, and so are crude and inaccurate. Thus, if the rate of anaesthetic drug administration is titrated to achieve a similar set of physiological parameters such as heart rate, blood pressure, or respiratory rate, then it is probably incorrect to assume all patients are all at a similar depth of anaesthesia. For

example, at a blood pressure of 90/50, an elderly patient with a history of hypertension and blood pressure is likely to be deeply anaesthetised whereas a pregnant young woman could be awake!

Secondly, calculation of the BIS involves a processing delay – the BIS value at any given moment represents a summary of cortical activity during the previous 15 to 60 sec. This will introduce a degree of error during periods when depth of anaesthesia is changing. The rate of change in the clinical state is important too. In some patients in whom anaesthesia was induced with a large dose of propofol, the BIS was initially >90 after loss of consciousness, but then plummeted rapidly to 20's or 30's seconds later. The more rapidly anaesthesia is induced, the faster the clinical state will change, and the greater will be the differential between successive EEG epochs being analysed. Also when there are rapid changes in clinical state, the timing of clinical testing becomes more important – any delays can introduce significant inaccuracy. When short-acting agents are used, recovery from anaesthesia will also be very fast. For the majority of the patients in this series, anaesthesia was maintained with infusions of propofol and remifentanil. Many of these patients remained apnoeic until just after return of consciousness – during the recovery phase the clinical status of many patients changed from apnoeic and unconscious to awake and speaking within 5 sec! Thus it was that some patients opened their eyes while BIS was low, only for it to rise to high values (80's or 90's) seconds later.

Another reason for the variability in the BIS is that the processing delay itself is variable. If the signal quality is good the BIS will reflect the more recent status of the patient. But if, for example, the patient is talking (as may happen during induction of anaesthesia), or the patient is grimacing, frowning or moving their eyes (during induction or recovery), the monitor will recognise the EMG activity as artefact and

suspend processing, so that the BIS values shown represent cortical activity present 60 seconds previously. This is illustrated in Figures 11.2 and 11.3. In both cases it can be seen that just before loss of consciousness there is a blank section in the BIS trend indicating that the signal quality was so poor that processing was suspended. As consciousness was lost, the patient stopped speaking or moving, allowing processing to be resumed. There was thus a sharp fall in the BIS soon after loss of consciousness.

During anaesthesia there is considerable moment-to-moment variability in the BIS. In my experience this short-term variability is reduced by the administration of larger doses of opiate (this is also mentioned in the product literature, but not referenced). Short-term small changes in the BIS (<10 BIS units) may represent short-term changes in cortical activity, but more likely probably represent minor, possibly random, clinically insignificant changes in bicoherence among the component frequencies in the frequency spectrum, and in the frequency spectrum itself.

Despite the inter-individual BIS variability at different clinical end points, and the short-term fluctuations in BIS values, the trend in individual patients is significant. In Figures 11.2 and 11.3 it can be seen that, with the exception of the moments during loss and return of consciousness, there is a large difference between the conscious and unconscious BIS values. With some short-term variation the BIS remained at approximately 40 in the patient undergoing total intravenous anaesthesia, whereas the BIS remained in the region of 60 in the patient undergoing inhalational anaesthesia. In both patients there was a clear and significant upward trend in the BIS prior to return of consciousness. It is also interesting to note that in the first patient, in whom the BIS was close to 40 during the operation, return of consciousness took longer than it did in the second patient – in the first patient the interval between end of surgery (when anaesthetic agent administration ceased) and response to voice was 5 min whereas in the

second patient this interval was 3 min. Given that neither patient was administered a long-acting drug, it is likely that the BIS was correctly indicating that anaesthesia was maintained at a deeper level in the first patient.

A steep, sustained rise in the BIS in any patient cannot be ignored. The BIS recordings shown in figures 11.2 and 11.3 were typical of the cohort: a sustained rise in the BIS was followed soon after by a return of consciousness; or in some cases a return to consciousness was followed soon after by a sharp sustained rise in the BIS. A recent case of awareness with recall during a general anaesthetic for cardiac surgery was associated with sustained increases in the BIS to levels between 60 and 75.[150]

Awareness is not always associated with explicit recall. Of the 110 patients studied, all regained consciousness in the operating theatre, yet only 14 actually remembered this. Of the 96 patients who, prior to leaving the theatre had sufficient return of their higher mental functions to be able to correctly state their date of birth, only 12 remembered regaining consciousness in the operating theatre. In the patients studied new memory functions returned somewhat later than other mental functions associated with consciousness – by the time patients were transferred to the recovery ward visual, auditory and reasoning processes were seemingly intact, yet in most new memory formation was delayed for a further period of time. Interestingly the presence of pain was not associated with a greater likelihood of early return of new memory formation.

During a study of 14 volunteers sedated with propofol Leslie found that the BIS was able to predict loss of memory (for words) – the BIS associated with 50% suppression of learning was 91.[151] In the current study this association was not present on recovery from anaesthesia. The BIS values recorded when the patients were able to state their date of birth do not predict whether or not the patient will later remember

being conscious at that time. Of the 14 patients that correctly thought they had regained consciousness in the operating theatre, 12 had been able to state their date of birth prior to leaving the operating theatre, at which time the median BIS value was 88 (range: 64 – 98). Of the 96 patients who thought that they had woken up in the recovery room or later, 86 had been able to state their date of birth before leaving the operating theatre, at which time the median BIS value was 89 (range: 69 – 98).

In the patients studied the median (inter-quartile range) BIS values at intubation, start of surgery and end of surgery were 43 (38 – 52), 48 (40 – 55) and 52 (45 – 60) respectively. This is in keeping with the recommendations of Aspect Medical Systems, the manufacturers of the A-1000™ and A-2000™ BIS monitors that the BIS should be kept between 40 and 60 during surgical anaesthesia. However, in later studies of patient-controlled sedation (chapters 13 and 14), BIS values between 55 and 60 were recorded in several volunteers who were conscious. Thus, it is probably safer to target BIS values between 40 and 50 during surgical anaesthesia.

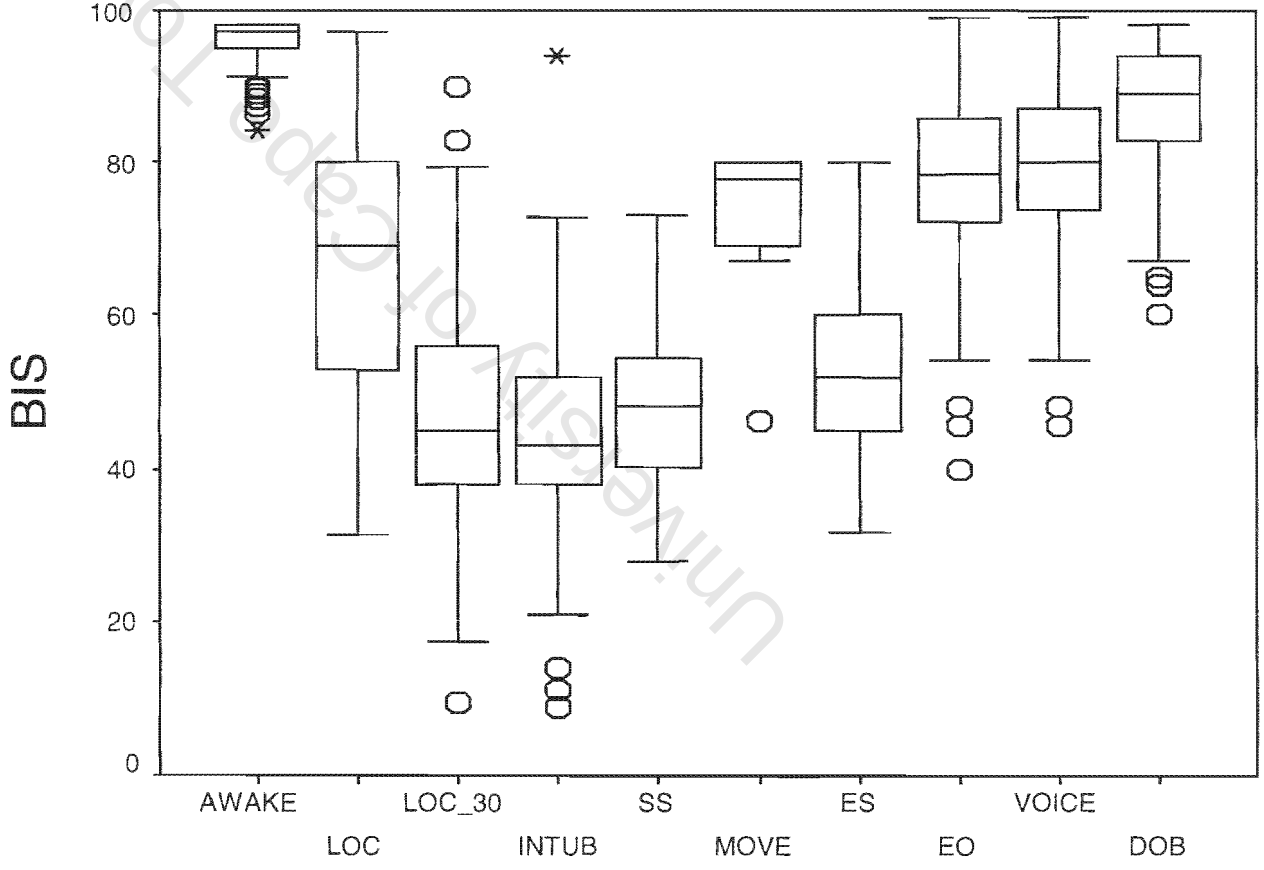


Figure 11.1: Summary of BIS values recorded at the time of different clinical events: Awake: before administration of any anaesthetic agents, LOC: at loss of eyelash reflex, LOC_30: 30 sec after LOC, SS: start of surgery, ES: end of surgery, Voice: at first response to voice, EO: at first eye opening, DOB: when patient was able to state date of birth, MOVE: if patient moved. Boxes represent the median and inter-quartile range (IQR), whiskers the range of values (excluding extremes and outliers), circles represent the outliers (data items 1.5 to 3 multiples of the box height above or below the upper or lower margin of the box) and stars the extreme values (outside of outliers)

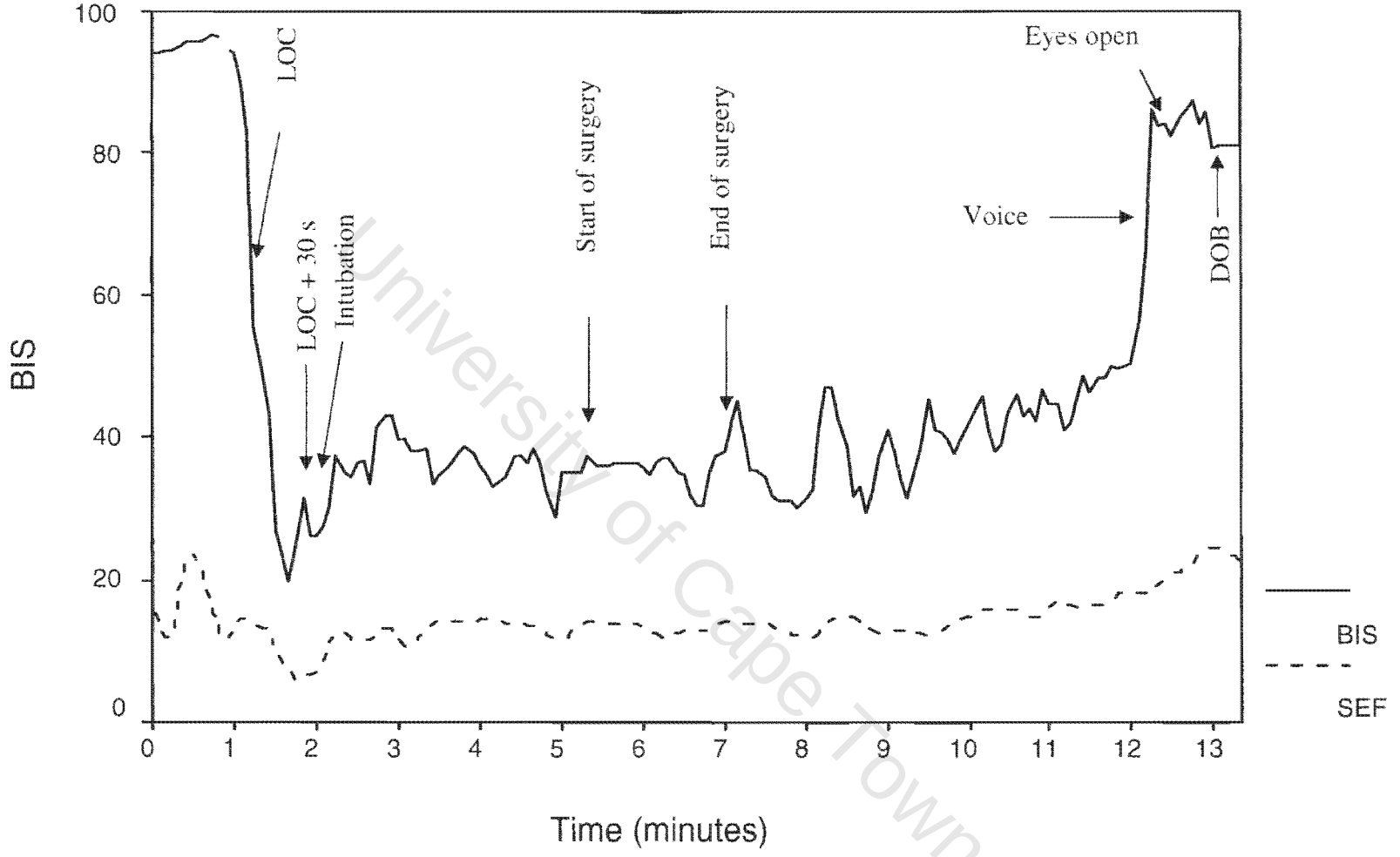


Figure 11.2: BIS data recorded electronically from a patient undergoing a sigmoidoscopy under intravenous anaesthesia using infusions of propofol and remifentanil

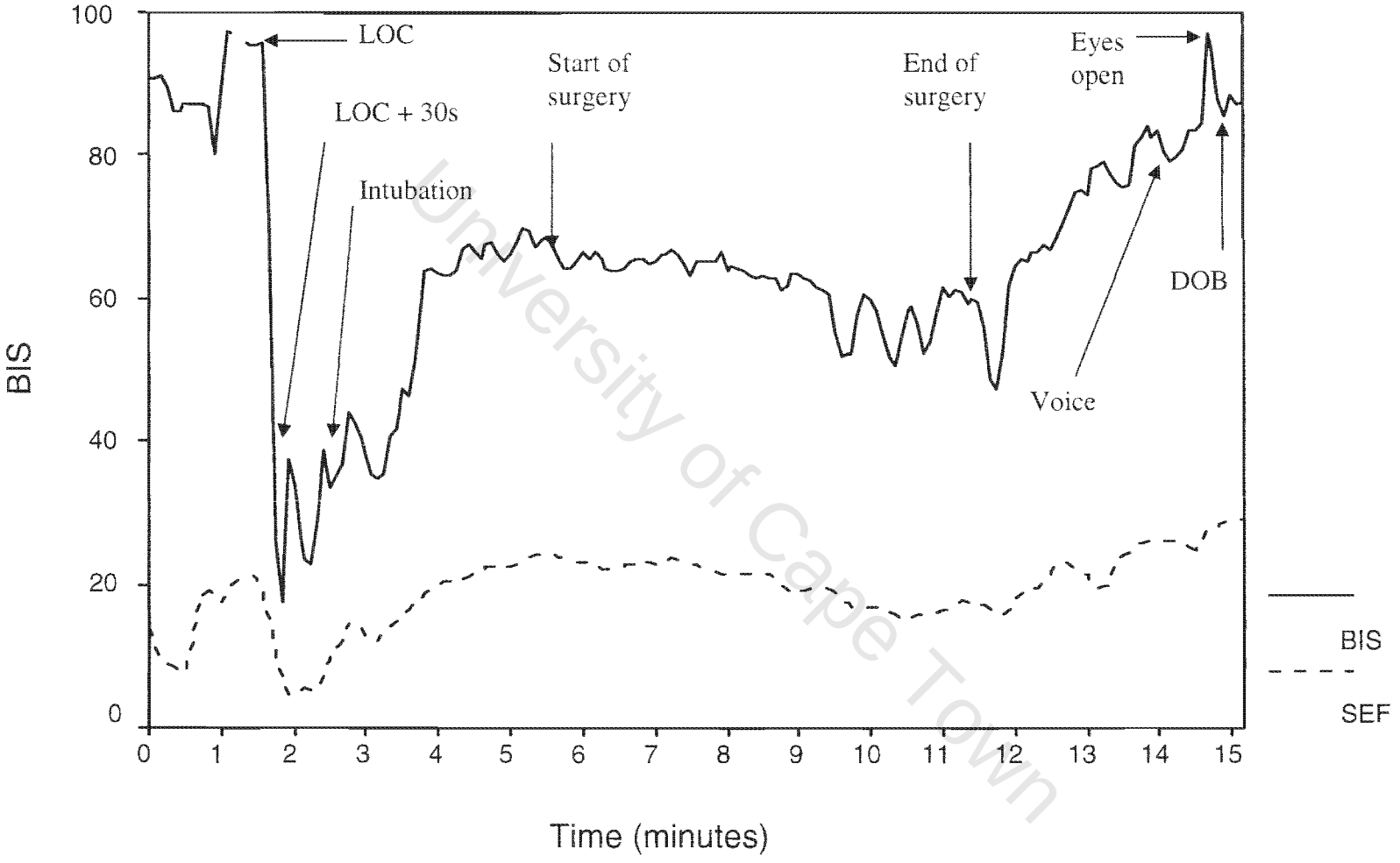


Figure 11.3: BIS data recorded electronically from a patient undergoing a sigmoidoscopy under inhalational anaesthesia with isoflurane and nitrous oxide

Table 11.1: Summary of data relevant to where patients thought they were when they regained consciousness. Numbers in the last column represent median BIS values at which the patient was first able to correctly state their date of birth after anaesthesia. All other numbers represent the number of patients in each category.

Where did patient think he woke up?	Pre-medication?		Induction		Maintenance		Median BIS when DOB stated
	Y	N	IV	Volatile	IV	Volatile	
Theatre (N = 14)	4	10	14	0	11	3	88
Recovery (N = 85)	8	77	84	1	68	17	89
Ward (N = 10)	3	7	10	0	7	3	85
Don't know (N = 1)	0	1	1	0	0	1	(90)

Chapter 12

Project 3: **Effects of the clicks of an AEP stimulus on the BIS**

BACKGROUND

Many studies have sought to validate the BIS by comparing it with other indicators of anaesthetic depth during the course of anaesthesia or sedation. Variables commonly used for comparison are clinical variables such as the heart rate and blood pressure, blood propofol concentration, spontaneous EEG variables such as the MF and SEF, and parameters derived from auditory evoked potentials (such as Na or Nb latency or amplitude, or the AEPindex).[92;132;136;152;153]

To generate an auditory evoked potential, it is necessary to subject the patient to repetitive loud auditory stimuli, usually in the form of clicks at an intensity that some people find uncomfortable (70dB above the hearing threshold). These auditory stimuli are usually presented at a rate of approximately 7 Hz (which is at the boundary between the classical theta and alpha EEG bandwidths) a frequency found in most EEG recordings other than when deep anaesthesia or neuro-pathology cause an isoelectric EEG.

At the time when the studies for this thesis were being planned, I and other investigators were considering studies during which the BIS and AEPindex would be recorded simultaneously. It was thus important to investigate the possible influence of the AEP clicks on the BIS. Theoretically two main mechanisms of interaction are possible. Firstly, as the clicks are loud (and painful for some subjects) they have the potential to directly increase conscious levels, especially during light sedation, in the

same way as any other noxious stimulus may cause arousal. Secondly, by subjecting the patient to regular, repetitive stimuli, it is possible that these stimuli may generate some degree of resonance or at least waveforms or harmonics related in phase and frequency to the auditory stimulus. This is more likely during surgical planes of anaesthesia when there is synchronisation and general slowing of the EEG.

The aim of the study was thus to determine whether or not such interactions occur in clinical practise, and if so how significant they are.

METHODS

Patients

Ethics committee approval was sought and granted. Ten adult patients who gave informed consent where enrolled. All were ASA status I, and were scheduled to undergo elective plastic or lower limb orthopaedic surgery. Exclusion criteria were impaired hearing, obesity (weight > 100 kg, or body mass index > 30), hiatus hernia or significant gastro-oesophageal reflux, and psychiatric disorders. Anxious patients requiring sedative premedication were also not considered.

Equipment

An A-2000™ BIS monitor (software version 3.3) was used to calculate the BIS data, which were recorded electronically every 5 sec using the BISCLAN system in "monitor only" mode as described in chapter 9. A custom-made AEP system, developed in Glasgow and used in numerous studies, was used to generate clicks at a frequency of 6.9 Hz and volume of 70 dBHL. AEP waveforms were not recorded.

Study protocol

A "clasp-knife" type design was chosen with each subject acting as his own control. The BIS was recorded during 6 epochs of 5 min each, during which the clicks of the AEP system were alternately switched on or off. The epoch length was chosen empirically – it was thought that conscious levels, and EEG phenomena would probably return to steady state within 1 or 2 minutes of a change (i.e. clicks switched on or off), leaving a further 3 or 4 minutes for recording the BIS.

For the first 15 min of the study the patients were sedated. The final 15 min of the study were performed after the patient had been anaesthetised. Patients were assigned study numbers in the order in which they were recruited. Patients whose study numbers were 1, 3, 5, 7, and 9 had the clicks on during odd-numbered epochs, and off during even-numbered epochs, while the reverse applied to the patients with even study numbers.

On arrival in the pre-anaesthetic care unit (PACU), routine monitoring was instituted (heart rate, non-invasive arterial pressure, and oxygen saturation) and continued for the duration of the study. Measurements were manually recorded every 5 min. A 20G intravenous cannula was inserted into a vein on the dorsum of the non-dominant hand, through which a target –controlled infusion (TCI) of propofol was administered. The 3 patients scheduled for lower limb orthopaedic surgery first had a lumbar epidural catheter inserted. Bupivacaine 0.5%, 10 ml, was injected into the epidural space, and the patient was observed for 20 min before the propofol TCI was started. During this period, 500 ml of Geloflex (B. Braun Medical Ltd, Sheffield, UK) was administered. There were no episodes of hypotension (prospectively defined as systolic blood pressure < 80 mm Hg, or a decrease of >30% from baseline).

The TCI was delivered by a Fresenius Master TCI pump (Fresenius Vial, Brezins, France) incorporating the Diprifusor pharmacokinetic microprocessor (AstraZeneca, Macclesfield, UK). The initial target propofol concentration was 1 μg/ml. A single investigator assessed sedation levels using the responsiveness portion of the modified Observer's Assessment of Alertness/Sedation score (OAA/S)[107] every minute. The target propofol concentration was gradually increased until the OAA/S score was 4 (response to name spoken in normal tone), and the patient was lying peacefully, with closed eyes. The target blood concentration was then set to the current estimated effect-site concentration. Once the blood and effect-site concentrations had equilibrated, the first 15 min of BIS recording was started. The amount of noise in PACU was kept to a minimum, and the patient was not disturbed except to assess sedation and measure arterial pressure.

At the end of the first 15 min, the propofol TCI was continued at the same target, and the patient was moved into the operating theatre. After he or she had breathed 100% O_2 for 3 min, anaesthesia was induced and maintained with the propofol TCI, supplemented with a remifentanil or alfentanil TCI (targets 4ηg/ml and 50 ηg/ml respectively) in patients undergoing plastic surgery. A laryngeal mask airway (LMA) was inserted and the patients' lungs were mechanically ventilated using 40% O_2 in air, except for the orthopaedic patients who breathed the same mixture spontaneously. In the mechanically ventilated patients, volume-controlled intermittent mandatory ventilation was used, with tidal volumes of approximately 8 ml/kg, and the frequency adjusted to maintain normocapnia. The target propofol concentration was reduced to a level 10% above the estimated effect-site concentration required for loss of consciousness and LMA insertion. After equilibration, the target concentrations of propofol and opioid

were kept constant, and the second 15 min period of BIS recording began. The study terminated at the end of this period, and the surgeon was invited to start the operation.

Statistical analysis

OAA/S scores are presented as median (range), and all other data as mean (standard deviation). For individual patients median OAA/S scores and mean BIS values were derived by combining epochs during which the clicks were respectively on and off. All 5 OAA/S scores for each epoch were included, whereas only the middle (3^{rd}) minute of BIS data from each epoch was used, to ensure that only BIS values derived from EEG data recorded during the current epoch were included (the processing delay can be up to 60 sec), and that the effects of the state change had subsided. Two-way ANOVA was used to assess the effect of the clicks on the BIS. OAA/S scores were compared using the Wilcoxon rank-sum test. $P < 0.05$ was regarded as statistically significant. Data were summarised and analysed for significance using SPSS statistical software (SPSS Inc, Chicago, USA).

RESULTS

Five males and 5 females were studied. Mean age, weight and height were 39.8 (20.3) years, 68.3 (17.1) kg and 168 (13.3) cm respectively. The mean effect-site propofol concentrations required for sedation and maintenance of anaesthesia were 1.6 (0.4) and 3.6 (1.0) $\mu g.ml^{-1}$ respectively. During sedation the median OAA/S scores were 4 (3 - 4) with the clicks on, and 4 (3 – 5) with the clicks off ($P > 0.37$). There was no difference between OAA/S scores in the first minute after starting the clicks compared with subsequent minutes. During general anaesthesia, stopping or starting of the clicks was not associated with a change in heart rate or blood pressure. One patient, who was only

receiving propofol, moved intermittently during the 2nd, 3rd and 4th minutes of the 6th epoch, during which the clicks were off. During this time the BIS was between 70 and 80. The movements stopped without any change in target propofol concentration. His data were included in the analyses.

Mean BIS values during the 3rd minute of each epoch for individual patients are shown in Figure 12.1. BIS data were not collected for one patient during epoch 6, as the study was terminated when the surgeon insisted on starting the operation. There was broad variation in recorded BIS values found despite the fact that the anaesthetic drug infusions were titrated to the same clinical endpoints in all patients. All patients remained conscious during the 1st (sedation) phase of the study, including two patients who had several successive BIS recordings between 55 and 60.

ANOVA showed that the presence or absence of the clicks was not associated with a statistically significant difference in the BIS (P = 0.8). During sedation, the mean BIS values were 75.2 (9.8) when the clicks were on and 74.9 (9.8) when the clicks were off. The mean within-subject difference in the BIS (value with clicks on less value with clicks off) was –1.4 (standard deviation 2.8)(95% CI for the mean: –3.2 to 0.4) during sedation. The between-subject variability in BIS data during sedation was far greater than the within-subject variability (mean sum of squares of errors 2411.6 versus 27.3; F = 88.3, P < 0.001).

During general anaesthesia the overall mean (SD) BIS value was 46.9 (15.0). Once again ANOVA showed that the presence or absence of the clicks was not associated with a statistically significant difference in the BIS (p = 0.4). The mean (SD) BIS values were 46.1 (13.7) while the clicks were on and 47.7 (16.3) while the clicks were off. The mean within-subject difference in the BIS (value with clicks on less value with clicks off) was –2.6 (standard deviation 9.2)(95% CI for the mean: –8.5 to 3.1) for

general anaesthesia. The between-subject variability in BIS data during general anaesthesia was far greater than the within-subject variability (mean sum of squares of errors 4120.0 versus 97.7; $F = 42.2$, $P < 0.001$).

When the BIS values for the full 5-minute duration of each epoch are analysed, the results are similar.

DISCUSSION

Although only 10 subjects were studied a large amount of BIS data was gathered. BIS data were recorded every 5 sec from each patient while sedated for a total of 75 min (15 epochs) during which they were subjected to AEP clicks, and a further 75 min (15 epochs) during which they were not. BIS data were then recorded from the same patients whilst under general anaesthesia for a further 75 min with the clicks on, and 70 min (14 epochs) with the clicks off. Despite this no evidence of an effect of the AEP clicks on the BIS or on clinical signs of anaesthetic depth, was found.

There are various reasons why the AEP clicks may not have an effect on the BIS. Probably the main reason is that the amplitude of the AEP signal arriving at the cerebral cortex is many orders of magnitude smaller than the background EEG (that is why signal averaging techniques are necessary to extract the AEP waveform from the EEG). Thus, unless there is resonance, the AEP signal is unlikely to impact on the power spectrum detected by the BIS monitor. The second possible reason is that even if the AEP clicks are initially rather loud, the stapedius reflex quickly causes accommodation. This reflex attenuates the amplitude of the electrical impulses passing along the auditory pathways. Moreover, although some subjects initially complained

about the loudness of the clicks, the study did not begin until the propofol TCI had been titrated to an OAA/S score of 4, and they had stated that they were comfortable (i.e. the clicks were no longer causing discomfort).

Although a large number of BIS readings were recorded and analysed, there is a large moment- to-moment variation in the BIS, even during periods when there are no external stimuli and no clinically obvious changes in depth of sedation or anaesthesia. For the patients in this study, the standard deviation of the BIS during the 3rd, 4th and 5th minutes of the first epoch is typically between 2 and 3. This variability in the data weakens the power of the study. With 10 subjects, and α level of 0.05, the null hypothesis can only be accepted with power > 80% for mean within-subject differences in BIS of 4.8 during sedation and 11.6 during anaesthesia.[154] To exclude a difference of 2.8 during sedation or a difference of 9.2 during anaesthesia a sample size of at least 32 patients is required.[134 151]Although this study outcome may be a false negative, this is unlikely, because two other studies have since also failed to show evidence of an influence of the AEP clicks on the BIS: Doi during a study of sevoflurane sedation and anaesthesia,[131] and Struys during a study of propofol anaesthesia.[99]

Beside the moment-to-moment variability in the BIS there was also considerable between-patient variation in the BIS. Aspect Medical Systems, the manufactures of the BIS monitors, recommend BIS levels of between 40 and 60 during surgical anaesthesia. During the general anaesthesia phase of the study one patient (age 70) who showed no clinical signs of light anaesthesia (heart rate < 85, systolic blood pressure < 100) consistently has BIS values between 59 and 70. Of slightly more concern was the fact that two conscious patients consistently had BIS values <60. Tests of memory formation during this period would have been informative but were not performed. This finding, along with similar findings in patients undergoing sedation studies (chapters 17 and 18)

lead to the conclusion that when the BIS is used to guide or control general anaesthesia, it is safer to aim for a BIS in the range 40 – 50.

In conclusion, it is unlikely that the AEP clicks have any influence on levels of sedation or anaesthesia, or on the BIS. This lack of evidence of an interaction adds weight to the validity of past and future studies where the AEP is measured at the same time as other EEG variables.

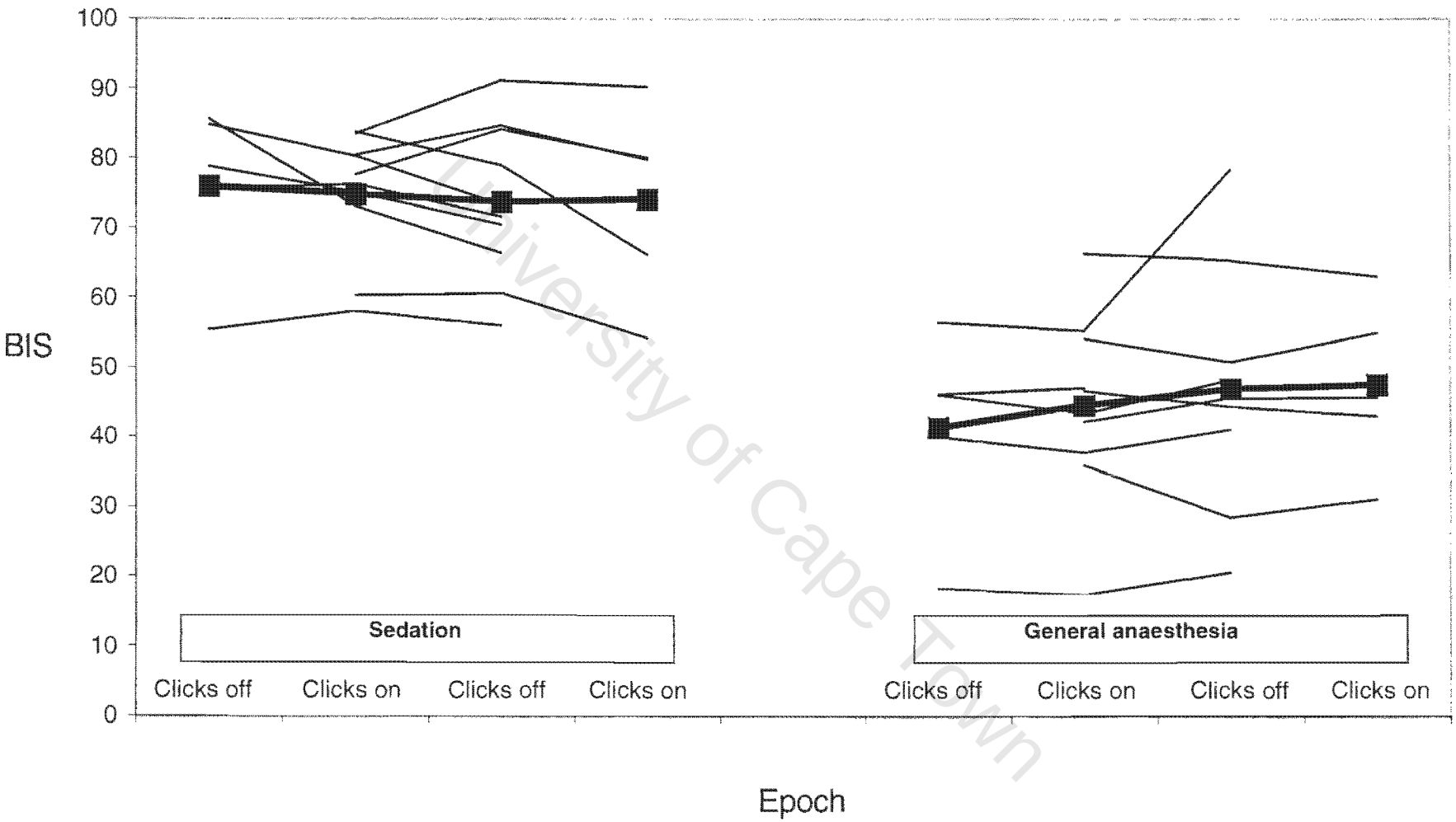


Figure 12.1: Mean BIS values for individual patients during 3rd minute of each epoch – the heavy line with markers represents the mean values

Closed loop control of general anaesthesia

Chapter 13

Project 4: **Closed-loop control of propofol anaesthesia during combined regional and general anaesthesia**

BACKGROUND

During the conduct of any general anaesthetic case, the anaesthetist is required to take note of numerous hundred data items. The categories of data are diverse and include the patient's clinical signs and physiological parameters; drugs doses, concentrations and stock levels; parameters related to the anaesthetic machine and gas supplies; data items relating to the surgeon and the surgery, and the time. At the same time there are many other distractions such as conversations; secondary tasks such as record keeping, drug and fluid prescriptions, teaching, the telephone and hunger!

Automatic feedback control of anaesthesia has many benefits. The system cannot be distracted, and is able to observe the control variable and make adjustments to the drug delivery rate more frequently than a human can. The high rate of adjustments to the control actuator, allied to the fact that these are made in a standard, calculated manner, make precise control and stability of the control variable more likely. As the dose is customised to meet the exact requirements of each individual patient, interindividual pharmacokinetic and pharmacodynamic differences can be overcome. A tailor-made dose or concentration profile offers the potential for limiting adverse effects, and improving the speed and quality of recovery. At the same time the risk of inadvertent awareness is also decreased. Finally, the objective and precise manner in which the dose is delivered makes a closed loop system an ideal research tool for

studies of drug interactions and of the effect of local and regional anaesthesia on anaesthetic drug doses.

Use of a variable in a closed-loop system also provides some information about the validity of that variable. If that variable can be used to provide stable control of the physiological process it is purported to measure, then it probably is a valid measure of the state of the system. As explained in chapter 10, the BIS is an EEG-derived measure that varies monotonically with anaesthetic depth. A BIS value of 100 indicates the fully awake state whereas 0 indicates no brain function.[143] Several studies, including that discussed in chapter 18, have shown a linear relationship between BIS and blood or effect-site propofol concentrations, [151] but it is not clear whether anaesthesia itself is a continuous, linear process (many components of anaesthesia demonstrate threshold effects, and the EEG demonstrates significant non-linearity). Although the BIS is increasingly used to assess anaesthetic depth in the USA and in Europe, it is seldom or never used in many UK hospitals [personal observation], and has failed to receive universal acceptance as the "gold standard" measure of anaesthetic depth.

The aim of this study was thus to determine whether, with the use of the BISCLAN system, it was possible to use the BIS to control anaesthesia automatically, and if so, to measure the performance of the system.

METHODS

After local Ethics Committee approval, and written informed consent, 10 adult patients presenting for elective major hip or knee joint replacement were enrolled. Inclusion criteria were ASA physical status I or II, and age 18 – 80 years. Exclusion criteria included body mass index > 30, neurological disease, and a history of use or abuse of psychoactive medication.

Anxious patients received 20 –30 mg of temazepam 1 hr before surgery. After arrival in the PACU, a 16-G cannula was inserted into a large forearm vein under local anaesthesia, and lactated Ringers solution was infused at 500 ml/hr. Routine physiological monitoring was commenced (pulse oximetry, non-invasive blood pressure, electrocardiography). After local anaesthetic infiltration with 1% lignocaine, an epidural catheter was inserted via the L2-L3 or L3-L4 interspace. A bolus of 10 ml 0.5% bupivacaine was then injected into the epidural space. Hypotension (defined as a systolic arterial pressure < 80 mm Hg or a > 30% decrease from baseline) was treated with ephedrine 3 mg bolus intravenous injections. The patient was observed for at least 20 min, during which time the upper level of epidural anaesthesia was determined by testing for cold sensation. When this level was at or above the T8 dermatome the patient was transferred to the operating theatre.

In the operating theatre two anaesthetists were involved with each patient. One took responsibility for the clinical care of the patient, and the other took care of the research equipment and manually recorded the relevant data every 5 min (these data included the BIS, physiological measurements, and the blood and effect-site propofol concentrations). On arrival in the operating theatre the patient was connected to the BIS monitor (A-1000, software version 3.2, Aspect Medical Systems, Newton, USA) of the BISCLAN system, which was started in monitor mode, and the electrode impedances were checked. If the impedance was > 5000 Ω the electrode was reapplied. After the patient had breathed 100% oxygen for 3 min, BISCLAN was switched to manual mode. Anaesthesia was induced in a structured manner using only propofol administered by the TCI system. The initial target blood propofol concentration was 2 µg/ml. This was then increased every 30 sec in steps of 0.5 µg/ml until consciousness was lost. A laryngeal mask airway was inserted, and the patient was allowed to breath 40% oxygen

spontaneously via a circle breathing system. Episodes of apnoea after induction were managed with gentle manual ventilation.

The surgeon was then invited to start the operation. After the start of surgery, once the investigators judged that the level of anaesthesia was adequate according to the usual clinical criteria (haemodynamic stability, no patient movement, regular and adequate spontaneous breathing, and no signs of autonomic activation), the BIS value was noted. BISCLAN was then switched to automatic (maintenance) mode, with that BIS value as the set point.

When the surgeon began the final sutures BISCLAN was switched to manual mode, with the target propofol concentration set to zero. All patients were kept in the operating theatre until they had regained consciousness and stated their date of birth. The times and BIS values present when the following events occurred were recorded manually: start of induction, loss of consciousness, laryngeal mask insertion, start of surgery, start of closed loop control, end of closed loop control, end of surgery, eye opening, first response to verbal command, patient able to state their date of birth.

All patients were visited during the post-operative period and asked to complete a questionnaire on memory, satisfaction and post-operative nausea and vomiting. These data were combined with those from patients involved in other studies and are reported in chapter 11.

Data analysis

Data were first tested for normality. Physiological data were normally distributed and are summarised as mean (standard deviation). Time intervals were skewed and are reported as median (range). Control performance was assessed by calculating the median prediction error (MDPE), median absolute prediction error (MDAPE), wobble

and mean offset. These measures were initially proposed by Varvel to assess the predictive performance of computer-controlled infusion pumps,[155] but they are equally useful for assessing control performance of feedback systems and have been used by other authors studying feedback control of neuromuscular blockade [156;157] and anaesthesia.[112] To calculate these measures it is first necessary to calculate the performance error (PE) for each measured BIS value as follows:

For the *j*th BIS measurement in the *i*th patient:

$$PE_{ij} = (BIS_{measured} - BIS_{setpoint})/BIS_{setpoint} \times 100$$

For the *i*th patient for whom N_i BIS values were recorded during automatic control MDPE, MDAPE and wobble are calculated as follows:

$$MDPE_i = \text{Median } \{PE_{ij}, j = 1, \ldots, N_i\}$$

$$MDAPE_i = \text{Median } \{|PE_{ij}|, j = 1, \ldots, N_i\}$$

$$Wobble_i = \text{Median } \{|PE_{ij} - MDPE_i|, j = 1, \ldots, N_i\}$$

Offset is calculated as: $BIS_{measured} - BIS_{setpoint}$. For each patient the mean offset was calculated. To summarise the overall offset the mean of the individual patient values was calculated. Offset and MDPE are measures of bias. MDAPE is a measure of inaccuracy (a low value indicates high precision whereas a high value represents poor or low precision). Wobble measures the intra-individual variability in performance errors. Summary values for MDPE, MDAPE and wobble represent the median (and range) of the values for individual patients – for example, in the current study in 10 patients, for MDPE the summary value is calculated as:

$$\text{Median MDPE} = \text{Median } \{ MDPE_i, i = 1, \ldots, 10 \}$$

RESULTS

Patient characteristics, duration of feedback control, and time intervals between the end of feedback control and eye opening, are summarised in Table 13.1. The BIS values, and estimated blood and brain propofol concentrations at key clinical events before and after automatic control of anaesthesia are summarised in Table 13.2.

The median duration of automatic control of anaesthesia was 72 (40 – 80) min. The target blood propofol concentrations chosen by the system during this time are shown in Figure 13.1. The minimum and maximum target concentrations during automatic control were 1.0 and 9.0 µg/ml respectively. These target concentrations resulted in satisfactory operating conditions in all but one patient. In this patient the system provided satisfactory conditions for the first 45 min of closed loop control. After this, 11 min before the end of the operation, the surgeon began to vigorously manipulate the hip joint, causing the whole patient to slide up and down, which in turn caused traction on the laryngeal mask airway which was fixed to the operating table via the breathing system. This sudden stimulus to an area not subjected to local or regional anaesthesia caused the BIS to rise from 50 to 84 in the subsequent 90 sec. Once the BIS reached these higher levels the patient began grunting and moving. The system responded appropriately and increased the target propofol concentration from 2.2 to 5.0 µg/ml. Soon afterwards the patient stopped moving, and the BIS decreased sharply to 34. At this stage the operation was almost finished, and so the system was switched to manual mode with the target propofol concentration set to 2 µg/ml. Performance data for this patient were included in the performance analysis.

Set point and system performance figures for individual patients are shown in Table 13.3. The median BIS set point chosen for closed loop control was 48 (40 – 57), median MDPE and MDAPE figures were 2.2 (-1.8 – 6.7)% and 8.0 (4.4 – 14.5)%

respectively, median wobble was 7.3 (2.5 – 14.4)% and the median mean offset value was 1.2 (-1.5 – 3.3). Figure 13.2 shows the offset values for all patients during automatic control of anaesthesia.

Cardiovascular parameters were stable for all patients throughout the period of automatic control (Figure 13.3). Oxygen saturation was > 95% at all times, mean respiratory rate was 18 (3) breaths/min, and mean end-tidal carbon dioxide partial pressure was 40 (7) mmHg. All patients were visited on the ward after their operation – none had evidence of explicit recall.

DISCUSSION

This study has shown that BIS-guided closed loop control of propofol anaesthesia is possible, and that the control performance of the BISCLAN system was satisfactory.

For periods lasting between 40 and 80 min, the system was able to provide clinically adequate anaesthesia in all patients, with good cardiovascular stability, and adequate operating conditions in all patients but one. For the patient that moved, the system responded appropriately. The fact that the patient did move is a reflection of the limitations of the control variable rather than a system failure. In any patient depth of anaesthesia is a dynamic balance between stimulation, hypnosis and analgesia. As there was no analgesia above the T8 dermatome, the system was required to administer a hypnotic, propofol, to limit or avoid responses to stimuli above this level. The sudden movement of the laryngeal mask in the pharynx and hypopharynx caused an abrupt increase in the patient's level of consciousness, as reflected by the rise in the BIS. The BIS gives an indication of the current hypnotic state, but in common with most EEG-based variables other than the AEPindex (later renamed AEP_{EX}), it is not able to reliably predict whether a patient will respond to a subsequent noxious stimulus.[131;132;158;159]

When the study was started there were no published reports of the use of BIS for closed loop control of anaesthesia or sedation. Although I didn't know it at the time, a group in Belgium lead by Prof. Michel Struys had also been developing and studying a BIS-guided closed loop system.[112;160] We were thus later able to compare results, which was particularly interesting because the Belgian system uses a different type of controller (an adaptive model-based controller, as opposed to a PID controller). In the current study the median bias (MDPE) was 2.2% indicating that the BIS had a tendency to be slightly greater than the set point value. The median inaccuracy (MDAPE) was 8.0% indicating that 50% of measured BIS values during automatic control were within 8% of the set point. Median wobble was 7.3%. These figures compared favourably with those found by Struys in his study comparing closed loop with manual control of anaesthesia.[112] In the latter study, MDPE, MDAPE and wobble were –6.6%, 7.7% and 5.9% respectively in the closed loop group, and –6.1%, 18% and 7.1% in the group in which anaesthesia was controlled manually.

Other EEG variables have been used to control anaesthesia. Schwilden and colleagues used the median frequency to control TCI infusions of methohexitone,[90;161] propofol [89] and alfentanil.[91] Their system incorporated an adaptive pharmacokinetic and pharmacodynamic model-based controller. Basically, the model was adapted by altering two pharmacokinetic parameters. The system was able to control anaesthesia effectively, but was only tested in small numbers of subjects, some of whom were paralysed, making it difficult to assess adequacy of anaesthesia. Indeed, some of the non-paralysed subjects still had corneal reflexes during the period of supposed anaesthesia. Effectiveness of Schwilden's system was also handicapped by the limitations of the control variable. As he did not formally evaluate the control

performance of his system, it is not possible to compare control performance of the system with that of BISCLAN.

Kenny and Mantzaridis developed an AEP-based closed loop anaesthesia system, and have evaluated it's performance in 100 patients by calculating the proportion of time that the measured AEP was within 5, 10 and 15% of the target AEP value.[121] These figures and those calculated for the performance of BISCLAN in the current study are shown in Table 13.4. As can be seen in Table 13.4, control performance was better in the study of the AEP system, but the figures from the two studies are not directly comparable. Firstly the control variables are different. The BIS correlates more closely with the blood propofol concentration than the AEP, whereas the AEP exhibits much more of an "on-off" phenomenon.[92] Thus while the AEP may be better at differentiating between the conscious and unconscious state, it may be less sensitive to small changes in anaesthetic depth. Secondly, the same control algorithm was used in both systems, using constants specifically "tuned" for the AEP_{EX}. For optimal performance, the constants used in BISCLAN should have been re-tuned for the BIS. Thirdly, the patient characteristics, type of surgery and anaesthetic technique were different. Patients in the BIS study were older (mean age 67 versus 50 years), heavier (mean weight 79 versus 66 kg) and were undergoing major orthopaedic surgery as opposed to body surface surgery. Finally, in both studies propofol anaesthesia was maintained automatically, but in the BIS study, it was supplemented by epidural analgesia to T8, whereas patients in the AEP closed loop study received target-controlled infusions of propofol and alfentanil, and breathed 66% nitrous oxide, thereby making them less likely to respond to changes in the level of noxious stimuli.

How else do the input signals differ? The BIS evaluates spontaneous cortical electrical activity, whereas the AEP reflects activity throughout the electrical pathway

from the cochlea to the cortex (thus it probably also reflects activity in the reticular activating system). Moreover, as an evoked potential, the AEP is in effect a continuous test of response to stimulation. It is not surprising that in two studies the AEP was able, whereas the BIS, spectral edge frequency and MF were unable to predict movement in response to noxious stimulation significantly better than chance.[131;132;158;159] In another study of the BIS it was shown that the effect-site opiate concentration is a better predictor of the likelihood of a clinical response to a noxious stimulus, than the BIS, and the concentration of propofol or isoflurane, even at BIS values indicating light anaesthesia.[128] As patients in the current study were not given any systemic or inhaled analgesics, they were thus more likely to have short-term fluctuations in their depth of anaesthesia and in the BIS when stimulated above the level of epidural blockade.

Although clinical and operating conditions were satisfactory, in three patients there were oscillations of the BIS and target propofol concentrations (cases 4, 5 and 10 in Table 13.3). None of these patients showed clinical signs of inadequate anaesthesia, or cardiovascular instability. The worst oscillations were seen in case 10, whose MDPE and MDAPE were also the worst of all the patients (Figure 13.4). In this patient the initial BIS target was 57. After 46 minutes the target was decreased to 45, whereupon stability increased markedly. There are several possible reasons for this oscillation. The first is that the constants used by the control algorithm were not appropriate for this patient. Our system used fixed gain constants tuned for AEP closed loop control. Even if the constants had been tuned for the BIS, they would not apply to all patients. It is likely that smaller changes made less frequently would have resulted in finer control. Adaptive algorithms have the benefit of individualising the control parameters for each patient at run-time, and this may lead to improved control.

Any source of phase delay in a closed loop control system is likely to cause oscillation. The control actuator in BISCLAN is a *blood*-targeted TCI infusion system, whereas hypnotic agents have their effect in the brain, not in the blood. Transfer of drug from blood to brain (the "effect-site") is not instant – the time course of equilibration depends on several factors including the cardiac output, the physical properties of the drug and the blood-brain concentration gradient. [135] Billard has estimated that the blood/effect-site equilibration constant, k_{e0}, is 0.2 min-1,[162] whereas Schnider has estimated a time to peak effect for propofol of 1.6 min.[163] Based on these figures, the time to peak effect after a bolus dose of propofol is of the order 1.6 to 4.5 minutes.[164]

Thus when the control actuator is a blood-targeted TCI system there is a significant lag in effect-site concentration, and clinical effect, when the closed-loop system changes the target blood propofol concentration. Under certain circumstances the resulting phase delay and oscillation can be further exaggerated. For example, if following an increase in blood concentration, the BIS falls to below the set point (i.e. effect site propofol concentration is now too high), the system will gradually decrease the target blood propofol concentration from the current level. If the blood concentration was initially greater than the effect-site concentration, then the effect-site concentration (and the clinical effect) will increase until the blood concentration has dropped below that at the effect site. This will result in a greater undershoot in the BIS. Conversely, if the blood propofol concentration is below the effect-site concentration and the BIS rises above the target BIS level, the system will gradually increase the blood propofol target. Before the blood concentration surpasses that at the effect-site, the effect-site concentration will fall whereas it should be rising to counteract the increase in BIS. This will result in a large BIS overshoot.

The phase delay is greatest when the system decreases the target concentration. As mentioned previously a drug infusion is an asymmetric controller. The rate of change in effect-site concentration is always proportional to the blood-brain concentration gradient, but whereas the blood concentration can be rapidly increased (limited only by the maximum pump infusion speed, and the rate of in vivo mixing of the drug), the rate of decrease in the blood propofol concentration is usually slower, being limited by the rates of re-distribution and elimination.

Possible solutions to the problems of blood-brain equilibration delay include "effect-site steering" and effect-site targeting. The former solution was used in a subsequent study (see chapter 14) while Struys and colleagues have incorporated effect-site targeting in their closed loop system.[160] Whichever solution is used, the benefit remains greater during periods when the BIS is greater than the set point (i.e. an increase in effect-site concentration is required) than when the BIS is below the set point (i.e. a decrease in effect-site concentration is required, and the rate of change of the effect-site concentration is limited by drug metabolism and distribution).

In the current study instability or oscillation had a tendency to be more of a problem when the BIS set point was too high. During the course of subsequent patient-controlled sedation studies (see chapters 17 and 18) several subjects were conscious at BIS values above 50. Initially the set point for case 10 was 57. While displaying the clinical signs of adequate anaesthesia, this patient may only have been "lightly" anaesthetised. A small increase in stimulus would thus be likely to cause an arousal response, and a large increase in the BIS. This may explain the improvement in control stability in the patient once the BIS target in this patient was reduced from 55 to 45 (figure 13.4).

In conclusion, this study showed that closed loop control of propofol anaesthesia, using the BISCLAN system, in patients having orthopaedic surgery under combined general and epidural anaesthesia, is possible. Cardiovascular parameters were stable during automatic control, and operating conditions were adequate in all except one patient who moved in response to sudden stimulation above the level of epidural anaesthesia. Overall stability of the control variable was adequate, although there was some oscillation in a further three patients. Control performance parameters compared favourably with those found and later published by another group who used a BIS-guided adaptive model-based closed loop anaesthesia system.

Table 13.1. Summary of patient characteristics and time intervals.

Age, years	67 (11)
Gender, n, male:female	4:6
Weight, kg	79 (11)
Height, cm	168 (9)
Median duration of feedback control	72 (40 – 80)
Interval between end of feedback control and eye opening	10.5 (2 – 15)
Interval between end of surgery and eye opening	3 (-6 – 7)

Values shown are mean (standard deviation) for normally distributed data and median (range) for non-normally distributed data.

Table 13.2: BIS values and propofol concentrations at key events (Median [range])

	BIS	Cp_{CALC} (µg/ml)	Ce_{CALC} (µg/ml)
Baseline	97 [94-98]	0	0
Loss of consciousness	74 [53-89]	4 [3.5-7]	1.5 [1.1-3.3]
LOC + 30 seconds	59 [40-74]	Not recorded	Not recorded
Prior to intubation	58 [43-66]	4 [3.5-5]	1.9 [1.3-3.6]
Start of surgery	46 [34-67]	3.4 [2.8-4]	3.5 [2.8-4]
Start of automatic control	45 [40-57]	3 [2.5-4.5]	3.1 [2.6-4.5]
Eye opening	80 [67-87]	1.6 [0.7-2.2]	1.8 [0.9-2.9]
Responds to command	80 [79-87]	1.2 [0.7-2.2]	1.3 [0.9-2.9]
States date of birth	87 [80-91]	1.2 [0.7-2.2]	1.3 [0.9-2.5]

Cp_{CALC} = calculated blood propofol concentration (Marsh model)

Ce_{CALC} = calculated effect site propofol concentration (k_{e0} 0.26 min^{-1})

LOC = loss of consciousness

Table 13.3: BIS set point and performance parameters for individual patients

Case	Set-point	MDPE (%)	MDAPE (%)	Wobble (%)	Mean offset	Pre-medication
1	45	6.7	8.5	6.1	3.3	Yes
2	50	2.4	4.8	4.8	1.2	Yes
3	40	2.5	5.0	2.5	0.2	Yes
4	47	0.0	11.1	11.1	1.7	Yes
5	45	0.0	6.7	6.7	0.8	Yes
6	49	-1.8	8.2	9.0	-1.5	No
7	45	2.2	4.4	4.4	1.3	Yes
8	50	2.0	8.0	8.0	1.2	No
9	55	3.6	9.1	9.1	1.9	Yes
10	57	1.8	14.5	14.4	-0.7	Yes
Median	48	2.2	8.0	7.3	1.2	-

MDPE = Median performance error

MDAPE = Median absolute performance error

Table 13.4: Control of AEP_{Ex} and BIS as a percentage of total closed loop anaesthesia time

	AEP system[121]	BIS system
Within target value ± 5%	65	34
Within target value ± 10%	90	57
Within target value ± 15%	99	75

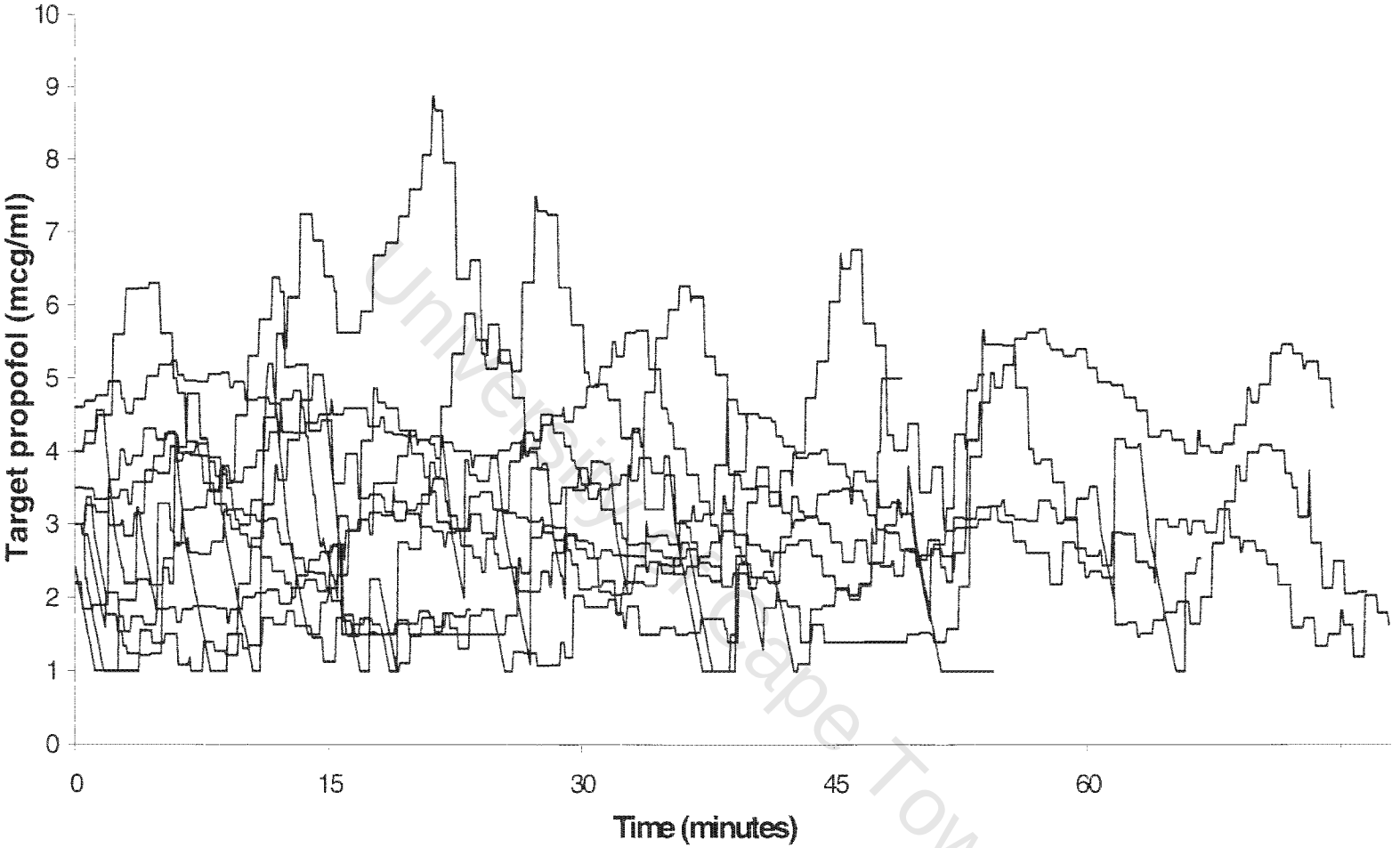


Figure 13.1: Target blood propofol concentrations (μg/ml) during automatic control of anaesthesia

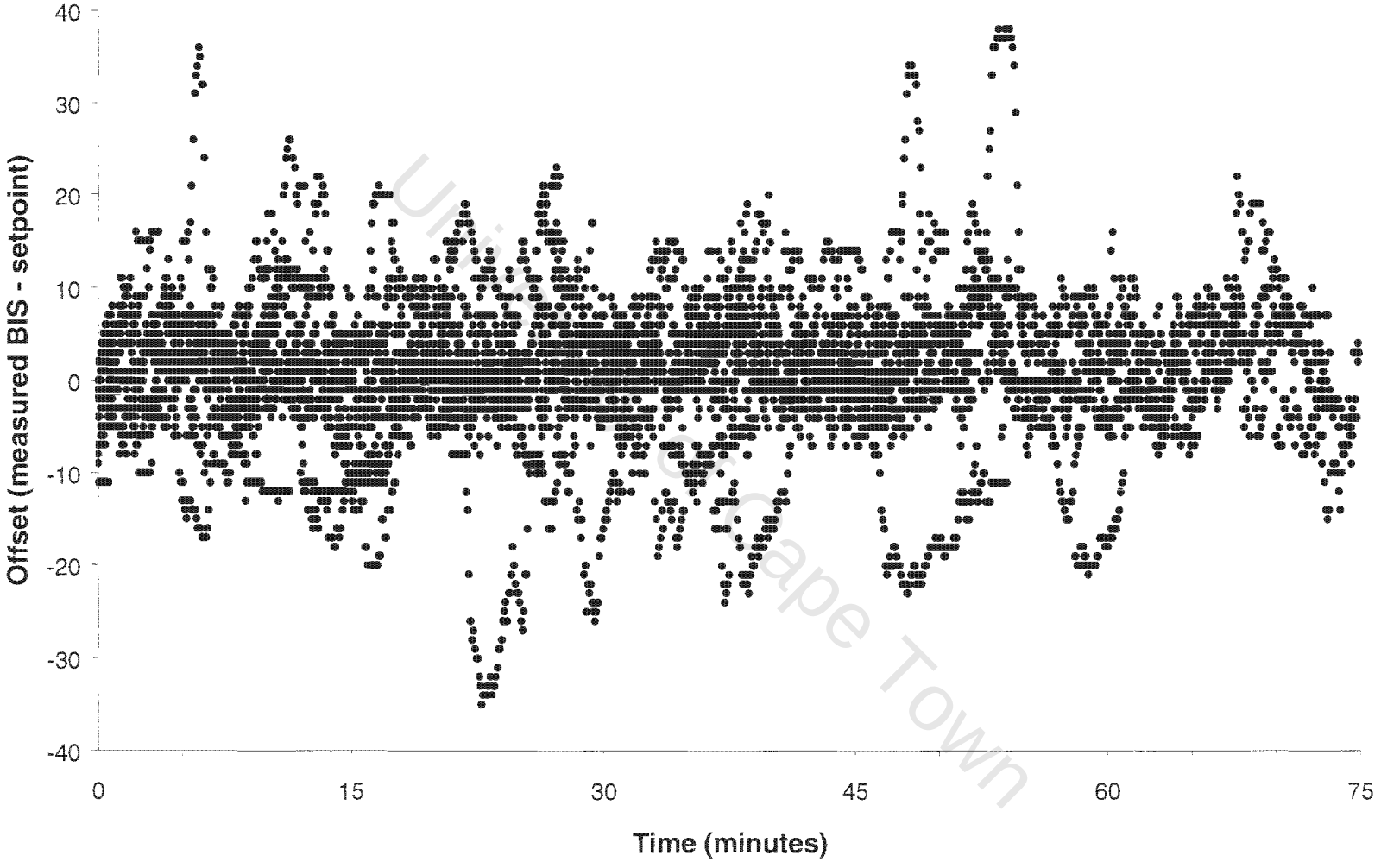


Figure 13.2: Individual offset values (measured BIS - set point) during automatic control of anaesthesia

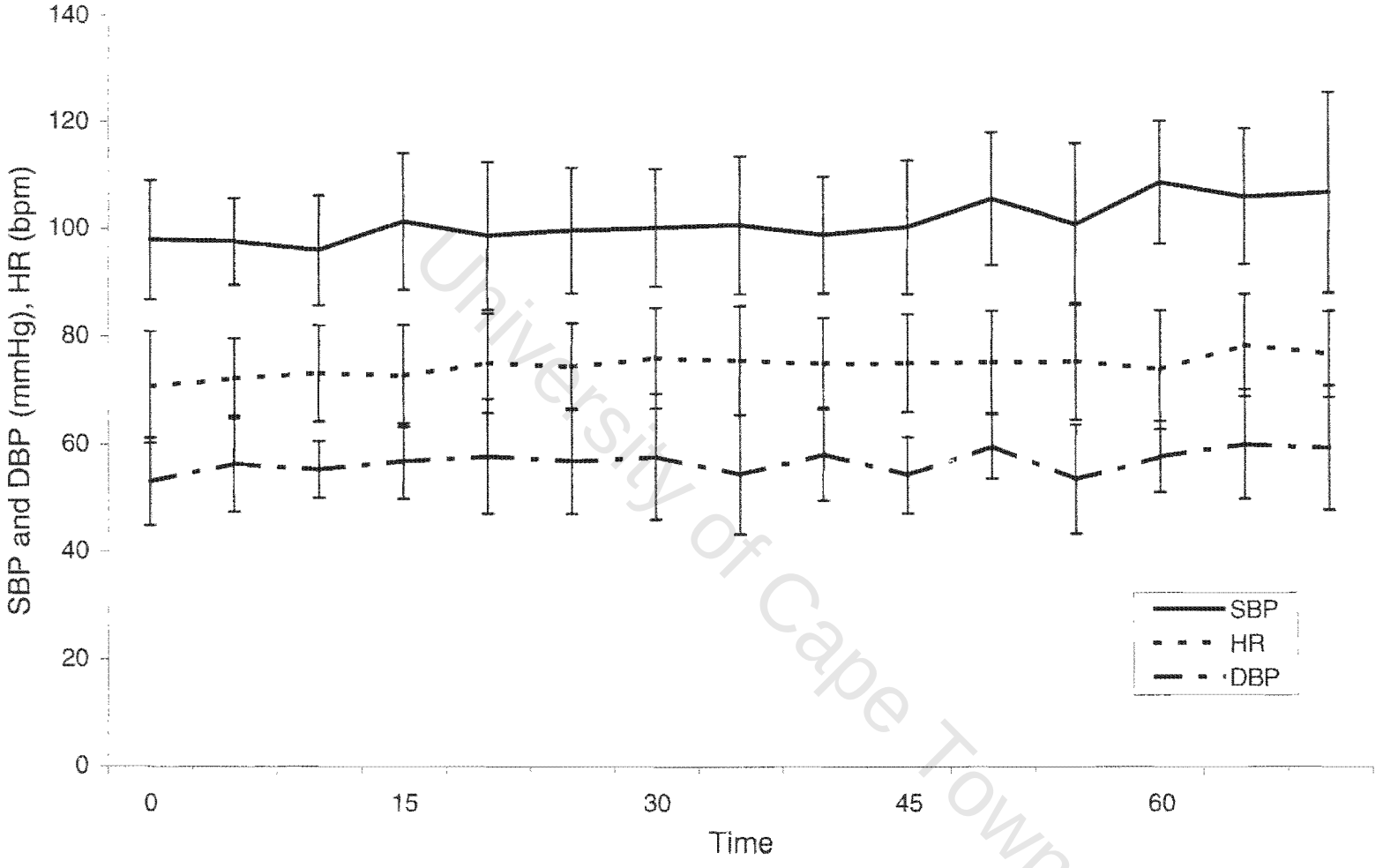


Figure 13.3: Haemodynamic parameters during automatic control of anaesthesia (mean (SD))

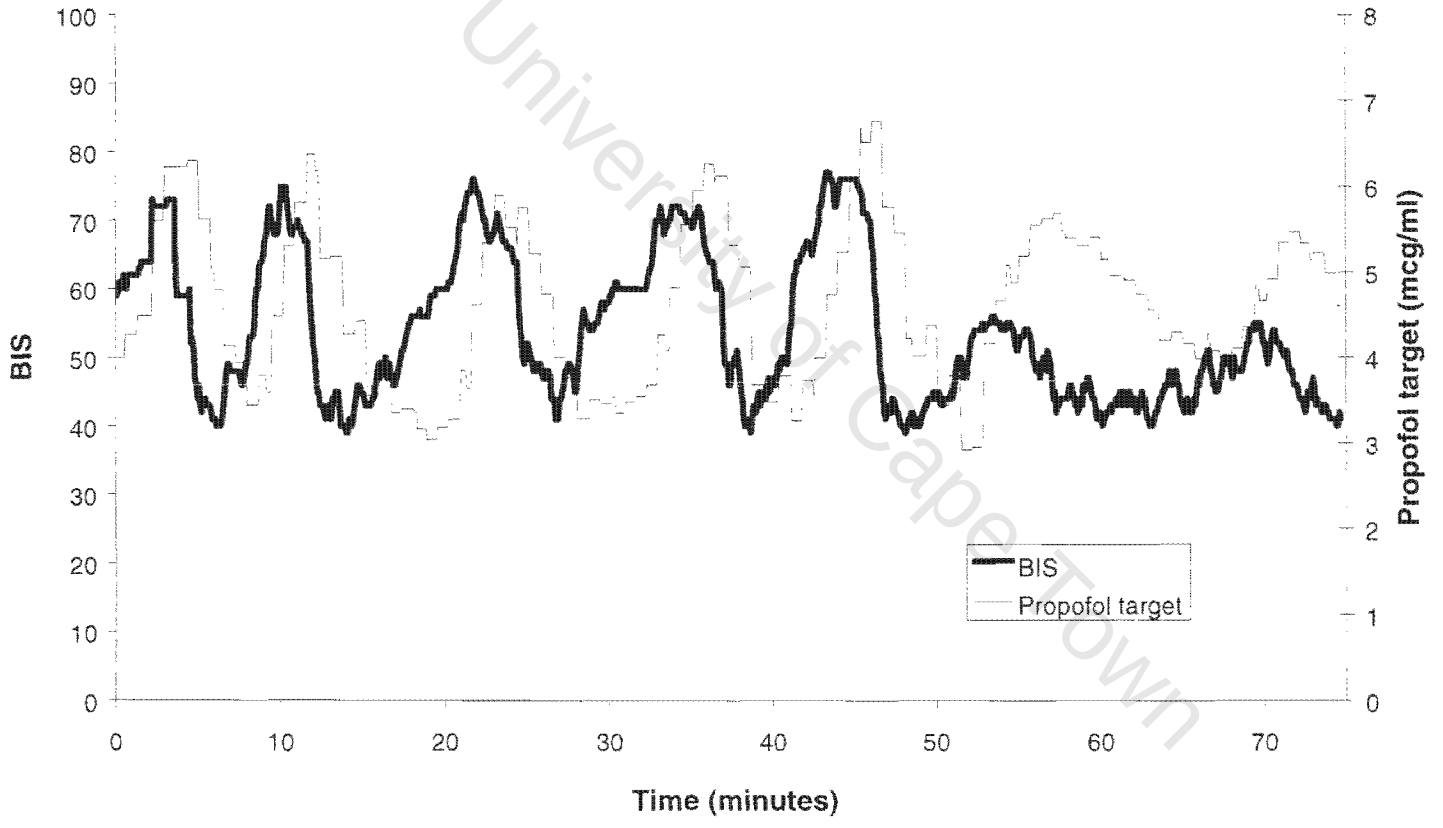


Figure 13.4: BIS and target propofol concentration (μg/ml) in case 10 during closed loop control of general anaesthesia

Chapter 14

Project 5: **Closed-loop control of propofol anaesthesia during propofol/remifentanil general anaesthesia**

BACKGROUND

In the previous study of BIS-guided automatic control of anaesthesia (Chapter 13), BISCLAN was tested in patients undergoing hip or knee replacement surgery, under combined general and regional anaesthesia. Although it was able to control anaesthesia, control was less than optimal, with oscillations in 3 patients and one patient moving when the hip was manipulated just before the end of the operation.

Because of these problems experienced during the first study, the system was revised as described below in the methods section. The aim of the current study was to assess the performance of the revised system, in a group of patients undergoing minor surgery, with analgesia provided by a remifentanil TCI (target concentration 4 ng/ml).

METHODS

Alterations to BISCLAN

The basic software and hardware comprising BISCLAN have been described in Chapter 9. As in the previous study, an A-1000 BIS monitor was used, but with a newer version (version 3.3, Aspect Medical Systems, Newton, USA). The exact changes incorporated in the newer BIS software were not made public by the manufacturers, although the company representative stated that the newer version had improved artefact handling capabilities, and was better able to deal with burst suppression (with previous software

versions there was sometimes a paradoxical increase in the BIS during EEG burst suppression).

With regard to the BISCLAN software, the programming and debugging interface and compiling software was upgraded from Delphi version 2 to version 4 (Inprise Corporation, Scotts Valley, CA, USA). In addition, small adjustments were made to the gain constants used in the control algorithm – the proportional gain constant, K_p, was decreased from 0.25 to 0.2, and the integral constant, K_i, was increased from 0.5 to 0.75. These changes were made on empiric grounds (no formal "tuning studies" were performed). Their aim was to reduce oscillation. A reduction in the proportional gain constant causes the system to make smaller changes to the target concentration in response to a change in the BIS. While the reduction in the proportional gain causes damping, it also has the potential to cause a greater overall bias. To offset this, the integral gain constant was increased. In all other respects the control algorithm was the same as that previously published, for the first 10 patients.

For the second group of 10 patients the control algorithm was altered to enable "effect-site steering" in an attempt to further reduce the problems of oscillation seen in the previous study. The aim of effect-site steering is to avoid some of the phase delay inherent in a blood-targeted TCI system by causing earlier and more accurate changes to the effect-site concentration, and also to limit the overshoot and undershoot in effect-site concentrations that occur during periods of oscillation. To achieve this, effect-site steering takes account of the error and the current predicted blood **and** effect-site drug concentration. Ordinary blood concentration targeting does not take account of the effect-site concentration.

Effect-site steering is implemented as follows. If the control variable is above the set point (i.e. depth of anaesthesia inadequate), the target blood drug concentration

will be increased. As with ordinary blood targeting, if the blood concentration is greater than that at the effect-site concentration, the system will implement small increments to the target blood concentration. If, however, the blood concentration is below that at the effect-site concentration, the system will immediately implement a larger increase in target concentration, to cause the target blood concentration to rise to a point above the estimated effect-site concentration. In these circumstances, in the absence of effect-site steering, a classical PID controller will simply increase the target blood concentration in small increments above the current level, which will result in an initial fall in the effect-site concentration, so that the control variable is likely to rise further above the set point. This will continue until the blood concentration is eventually increased to a level above that at the effect site.

The converse also applies. With effect-site steering, if the control variable is below the set point (i.e. depth of anaesthesia excessive), and the blood concentration is greater than the effect-site concentration, then the system will immediately implement a larger decrease in the target blood concentration, to a point below the estimated effect-site concentration. In the absence of effect-site steering, a classical PID controller will simply decrease the target blood concentration in small increments from the current value, which will result in an initial rise in the effect-site concentration, so that the control variable is likely to fall further away from the set point, resulting in even more excessive anaesthesia – only once the blood concentration has finally fallen to a level below that at the effect site will the effect site concentration start to fall, and the control variable start to increase toward the set point. In all other circumstances there are no differences between effect-site steering and blood concentraton steering.

The effect of these changes is illustrated in Figure 14.1 (a "screen dump" taken from BISCLAN after a period of closed loop anaesthesia). The software code for effect-site steering is shown in Appendix 7.

Clinical protocol

After local research ethics committee approval, and written informed consent, 20 adult patients presenting for body surface surgery were enrolled. To be included patients had to be of ASA status I or II, and aged between 18 and 80 yr. Exclusion criteria included body mass index > 30, a history of neurological disease and use of psychoactive medication.

No sedative premedication was used. As always, two anaesthetists were involved with each case – one was in charge of the clinical management of the patient, while the other took care of the research equipment and manually recorded the BIS, physiological data, and the blood and effect site propofol concentration every 5 minutes.

Anaesthesia was induced in the operating theatre. A 20-gauge cannula was inserted into a vein on the dorsum of the hand, and the patient was connected to the BIS monitor using four Zipprep electrodes (Aspect MS, Newton, USA) in the standard montage. Once it was confirmed that the electrode impedances were < 5000 Ω, and prior to attaching the patient to other monitors, BISCLAN was started in 'manual mode' with the target propofol concentration set at 1 – 2 μg/ml to provide some anxiolysis. Routine physiological monitoring was then commenced (pulse oximetry, electrocardiography, non-invasive blood pressure), and baseline values recorded, while the patient breathed 100% oxygen. The remifentanil TCI was then started (initial target concentration 2 ng/ml); and the propofol target was increased to 4 μg/ml in younger patients (< 70 years) and 2.5 μg/ml in the elderly (≥70 years). Every 30 sec until the

patient had lost consciousness and was able to tolerate laryngeal mask airway (LMA) insertion, the propofol target was increased by 0.5 µg/ml. Once the LMA had been inserted, the remifentanil target concentration was increased to 4 ng/ml and the lungs were mechanically ventilated with a 40% oxygen/air mix via a circle breathing system. The target propofol concentration was reduced to approximately 0.5 µg/ml above the estimated effect-site concentration noted during successful LMA insertion.

Once surgery had commenced a note was made of the BIS value at which the level of anaesthesia was clinically adequate (no patient movement, haemodynamic stability, absence of signs of autonomic activation). Automatic control of the propofol TCI was initiated using that BIS value as the set point. The remifentanil target concentration was left unchanged at 4 ng/ml. When the surgeon began the final skin sutures, BISCLAN was switched to manual mode, the target propofol and remifentanil concentrations were set to zero. Patients remained in the operating room until they had regained consciousness, the LMA had been removed and they had correctly stated their date of birth.

As in the previous study the time, BIS, and estimated blood and effect-site propofol concentrations present during the following key clinical events were recorded manually: loss of consciousness (eyelash reflex), just prior to intubation, just prior to skin incision, start of closed loop control, end of closed loop control, end of surgery, eye opening, response to command and patient able to state date of birth. The following data were recorded electronically every 5 sec: target BIS, estimated blood propofol concentration, BISCLAN mode, and the EEG-related data arising from the BIS monitor (including time, SEF, BIS, EMG power).

All patients were visited during the post-operative period and asked to complete a questionnaire on memory, satisfaction and post-operative nausea and vomiting. These

data were combined with those from patients involved in other studies and are reported in chapter 11.

Data analysis

Physiological data are presented as mean (standard deviation), and time intervals as median (range). As in the previous study system performance was assessed using the measures recommended by Varvel and colleagues: median prediction error (MDPE), median absolute prediction error (MDAPE), wobble and the mean offset. [155] These variables were tested for normality and found to be skewed, and are thus summarised in terms of the median and range of the values found in individual patients. The mean and 95% confidence interval of these values was also calculated, and these data will also be presented. Finally, the proportion of time (during automatic control) that the BIS was within 5, 10 and 15% of the set point was also calculated.

RESULTS

Patient characteristics, duration of feedback control, and summary of time intervals between the end of feedback control and eye opening, are summarised in Table 14.1. When compared with the patients in the previous study, these patients tended to be younger (mean age 42 versus 67 years) and to weigh less (mean weight 68 versus 79 kg). The gender ratio and heights were similar.

BISCLAN controlled anaesthesia automatically for a median duration of 27 (12 – 86) min in the current study. The resulting blood propofol concentrations during feedback control are shown in Figure 14.2. BIS values, and estimated blood and brain propofol concentrations, at key clinical events before and after automatic control of anaesthesia are summarised in Table 14.2. As mentioned in the methods section above,

patients received a low dose infusion of propofol for anxiolysis prior to induction of anaesthesia. Thus the median (range) effect-site propofol concentration at induction of anaesthesia was 0.3 (0.1 – 1.3) μg/ml. The median (range) BIS value associated with these concentrations was 97 (93 – 98).

Cardiovascular and respiratory parameters were stable in all patients throughout – cardiovascular data are summarised in Figure 14.3. Operating conditions were satisfactory in all patients, except for one, who moved for a brief period after the remifentanil infusion had been inadvertently left switched off after a syringe change. BISCLAN was kept in "maintenance" mode, and movement ceased when the remifentanil infusion was restarted.

The median (range) BIS chosen as the set point for automatic control was 50 (40 – 65). Figure 14.4 shows the offset values for all patients during feedback control of anaesthesia. Performance of the system in individual patients is summarized in Table 14.3, which also shows the median (range) of these individual values. The mean (95% confidence interval) of these performance parameters are: MDPE –0.42 (-1.4 to 0.6)%, MDAPE 5.6 (4.5 to 6.8)%, wobble 5.2 (3.8 to 6.5)% and mean offset –0.2 (-0.8 to 0.4). Performance was slightly better in those patients in whom effect-site steering was used (cases 11 – 20). In these patients the mean (95% CI) MDAPE, MDAPE, median wobble and mean offset were –1.39 (-2.8 to 0.0)%, 4.7 (3.4 to 5.9)%, 4.4 (3.1 to 5.7)% and –0.7 (-1.4 to 0.0). This compared with 0.6 (-0.8 to 1.9)%, 6.6 (4.7 to 8.5)%, 5.9 (3.4 to 8.5)% and 0.2 (-0.8 to 1.2) respectively in those (cases 1 – 10) in whom simple blood concentration targeting was used. The differences between control performance parameters with and without effect-site steering were not statistically significant.

The proportion of time during which the BIS was within 5, 10 and 15% of the set point is shown in Table 14.4. As shown in Table 14.4 there was a tendency for

greater accuracy of control in patients 11 – 20. Oscillation was only noted in one patient (case 4 in Table 14.3), in whom the BIS cycled between 45 and 62, while the blood propofol concentration cycled between 2.2 and 3.5 μg/ml. Despite this the heart rate and arterial blood pressure remained stable and the patient did not move in response to surgical stimuli.

All patients were satisfied with their anaesthetic, none recalled any dreams or noises and there was no other evidence of explicit recall.

DISCUSSION

In this study we assessed the control performance of the revised BISCLAN system in 20 patients undergoing body surface surgery, and found that it was able to keep the control variable (BIS) within satisfactory limits in terms of bias, precision and wobble. Haemodynamic variables were stable during automatic control of anaesthesia, and with the exception of one patient (where human error resulted in the patient moving for a short period), operating conditions were satisfactory in all patients.

As mentioned earlier, in my previous study of control performance of the BISCLAN system (chapter 13), oscillations were found in 3 out of 10 patients. In the current study, use of the revised system (smaller proportional gain constant, larger integral gain, and effect-site steering in the 11^{th} to 20^{th} patients) was associated with only 1 case of oscillation out of 20 patients. There was also a tendency for the control variables to be better: median values of MDPE, MDAPE, wobble and mean offset were 0.0, 5.0, 4.5, and –0.1 respectively in the current study, compared with 2.2, 8.0, 7.3 and 1.2 respectively in the previous study. However, it would be unwise to firmly conclude that the revised algorithm is better, as it was tested in a younger and healthier patient group under different surgical and anaesthetic conditions.

To my knowledge there are no published limits for acceptability of the bias and precision or inaccuracy of control systems in human studies. However, control performance in this study compares very favourably with that reported by others who have used similar methods of assessing performance. Using the BIS as control variable, an adaptive control algorithm, and an effect-site targeted propofol TCI, Struys and colleagues reported a MDPE of –6.6%, a MDAPE of 7.7% and median wobble of 5.9%.[112] The only other group to have studied and assessed feedback control of anaesthesia using the BIS was Morley and colleagues, who used a PID control

algorithm to control the *rate* of infusion of a mixture of propofol and alfentanil in 30 patients. [165] Morley and colleagues only performed a cursory assessment of control performance, although they did calculate the "median absolute unweighted residual," and found this value to be 6.8. Given that the set point was 50, this is equivalent to a MDAPE of 13.6%.

Studies of feedback control of neuromuscular blockade tend to produce somewhat better results. When an adaptive model-based feedback controller was used to control muscle relaxation using various drugs, median values of the MDPE, MDAPE, wobble and offset (%) all varied between –0.3 and 1.9%.[157]

When compared with the previous study, the percentage of time that the BIS was within 5, 10 and 15% of the set point in the current study was somewhat improved (46, 72 and 86% versus 34, 57 and 75% respectively – see Tables 14.4 and 13.4). These figures are not as good as those found by Kenny and Mantzaridis when assessing the performance of an AEP-based closed loop anaesthesia system (see Table 13.4).[121] The control algorithm used in their AEP system was identical to that used in the study discussed in the previous chapter. As mentioned in the previous chapter the figures from the AEP and BIS studies are not directly comparable.

Prior to starting automatic control of the propofol infusion, adequacy of anaesthetic depth was judged according to some of the traditional clinical signs of anaesthetic depth: lack of patient movement, haemodynamic stability, and absence of signs of autonomic activation. Although these signs are the measures used by most anaesthetists to judge the adequacy of anaesthesia in their day-to-day practise, they are neither sensitive nor specific predictors of the presence or lack of awareness. Thus it is hardly surprising that there was a broad range of BIS values associated with these conditions at the time of skin incision (29 to 72) and a broad range of values used as the

set point for automatic control of anaesthesia (40 to 65). Aspect Medical Systems recommend that the BIS is maintained between 40 and 60 in order to prevent awareness. It may thus be argued that the set point was too high in 2 patients (62 in one case and 65 in the other), and that higher set points may be associated with lesser stability of the control variable, the data from the current study do not support this. A more compelling reason for choosing a lower set point is the evidence from the sedation studies described in chapters 17 and 18, during which several conscious volunteers (responding to verbal command) recorded BIS values between 50 and 60. Although BIS values between 50 and 60 are unlikely to be associated with recall, to minimise the likelihood of awareness anaesthetists should probably aim to keep the BIS < 50 during general anaesthesia.

The possible reasons for oscillation were discussed in chapter 13. One of the chief potential reasons is the phase delay caused by the time-course of equilibration between the blood and brain propofol concentrations. When BISCLAN was being developed I would have preferred an effect-site targeted TCI system as the control actuator, but unfortunately the TCI systems we had in Glasgow could not implement effect-site targeting. The next best option was effect-site steering, which was implemented by adding a simple function to the BISCLAN source code (Appendix 7). Effect-site steering has the potential to make a feedback system respond more quickly and accurately than blood concentration targeting. In the current study the trend was for effect-site targeting to be associated with slightly worse bias, but improved precision and reduced wobble, although these changes do not reach statistical significance. A study with larger subject groups is required to test with adequate power, if effect-site steering is superior to simple blood concentration targeting.

Effect-site targeting is likely to be associated with the most precise control. With effect-site targeting the goal is to produce a specified effect-site concentration, rather

than a specific blood concentration (Figure 18.1). When an increase in target concentration is required, an effect-site targeted system will briefly increase the blood concentration to a level greater than the current and target effect-site concentration, to create a greater concentration gradient to "drive" drug into the effect-site. Conversely, when a target concentration decrease is required the system will allow the blood concentration to fall to below the target (effect-site) concentration, to generate a greater gradient so that the effect-site concentration will fall more rapidly. Effect-site steering is thus able to make more rapid and precise adjustments to the effect-site concentration, and thus to the clinical effect and the control variable.

In conclusion, BISCLAN was able to provide satisfactory control of propofol anaesthesia in patients having minor body surface surgery, with analgesia provided by a fixed blood concentration of remifentanil. Control performance, using the revised gain constants tended to be better than with the initial constants. Effect-site steering may also be associated with improved control performance, although the optimal control actuator is probably an effect-site targeted TCI system.

Table 14.1:. Summary of patient characteristics and time intervals.

Age, years	42 (12)
Gender, n, male:female	8 : 12
Weight, kg	68 (11)
Height, cm	169 (9)
Median duration of feedback control	27 (12 – 86)
Interval between end of feedback control and eye opening	8 (4 – 18)
Interval between end of surgery and eye opening	7 (3 – 12)

Values shown are mean (standard deviation) for normally distributed data and median (range) for non-normally distributed data.

Table 14.2: BIS values and propofol concentrations at key events (Median [range])

	BIS	Cp_{CALC} (μg/ml)	Ce_{CALC} (μg/ml)
Start of induction	97 [93-98]	1 [1 – 2.5]	0.3 [0.1 – 1.3]
Loss of consciousness	74 [50-91]	6 [4 – 8]	2.2 [1.1 – 3.9]
Ready for intubation	44 [28 – 69]	5.6 [3 – 8]	3.4 [2.1 – 5]
Ready for incision	51 [29 – 72]	4 [2.5 – 8]	3.9 [2.9 – 4.9]
Start of automatic control	50 [40 – 65]	3 [2.4 – 4.5]	3.3 [2.4 – 4.8]
Eye opening	74 [54 – 96]	1.3 [0.8 – 2.2]	1.6 [1 – 3.3]
Responds to command	77 [54 – 98]	1.2 [0.8 – 2.2]	1.6 [1 – 3.3]
States date of birth	92 [60 – 98]	1.2 [0.8 – 2.2]	1.6 [1 – 3.3]

Cp_{CALC} = calculated blood propofol concentration

Ce_{CALC} = calculated effect site propofol concentration

LOC = loss of consciousness

Table 14.3: BIS set point and performance parameters for individual patients

Case	Set-point	MDPE (%)	MDAPE (%)	Wobble (%)	Mean offset
1	40	2.5	5.0	0	0.9
2	50	0.00	4.00	4.00	-0.25
3	65	-3.08	7.69	7.69	-3.14
4	47	0.00	6.38	6.38	0.88
5	40	2.50	12.50	12.50	0.85
6	44	2.27	6.82	6.82	1.47
7	50	-2.00	8.00	8.00	-0.37
8	59	1.69	5.08	5.08	-0.43
9	41	0.00	7.32	7.32	1.89
10	62	1.61	3.23	1.61	0.49
11	58	0.00	5.17	5.17	0.16
12	43	0.00	2.33	2.33	0.47
13	40	0.00	7.50	7.50	-0.25
14	51	-1.96	3.92	3.92	-0.54
15	55	-3.64	3.64	3.64	-2.55
16	50	2.00	4.00	4.00	-0.03
17	55	-1.82	3.64	3.64	-0.74
18	55	-2.00	8.00	7.45	-0.88
19	50	-2.00	4.00	4.00	-0.76
20	45	-4.44	4.44	2.22	-1.91
Median	50	0.0	5.0	4.5	-0.1
(range)	(40 – 65)	(-4 – 3)	(2 – 13)	(0 – 13)	(-3 – 2)

Table 14.4: Control of BIS as a percentage of total closed loop anaesthesia time

	Blood targeted algorithm (n = 10)	Effect-site steered algorithm (n = 10)	All patients (n = 20)
BIS = set point ± 5%	43.3	49.7	46.2
BIS = set point ± 10%	65.7	79.4	71.8
BIS = set point ± 15%	79.4	92.9	85.5

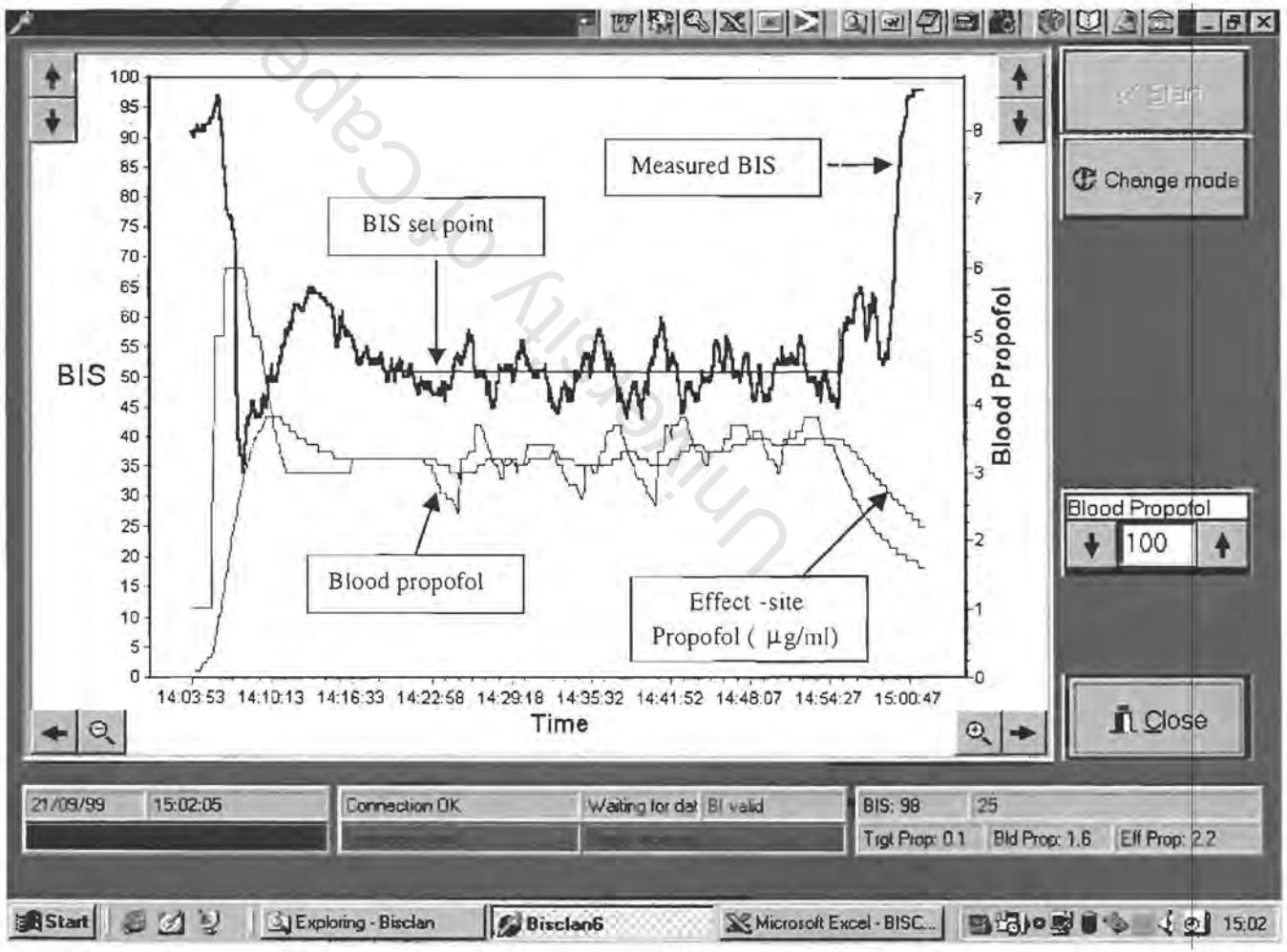


Figure 14.1: "Screen dump" from BISCLAN after a period of closed loop control, demonstrating effect-site steering. When changes to the target blood propofol concentration are required, the system takes account of the BIS error, and the current blood and effect-site concentrations.

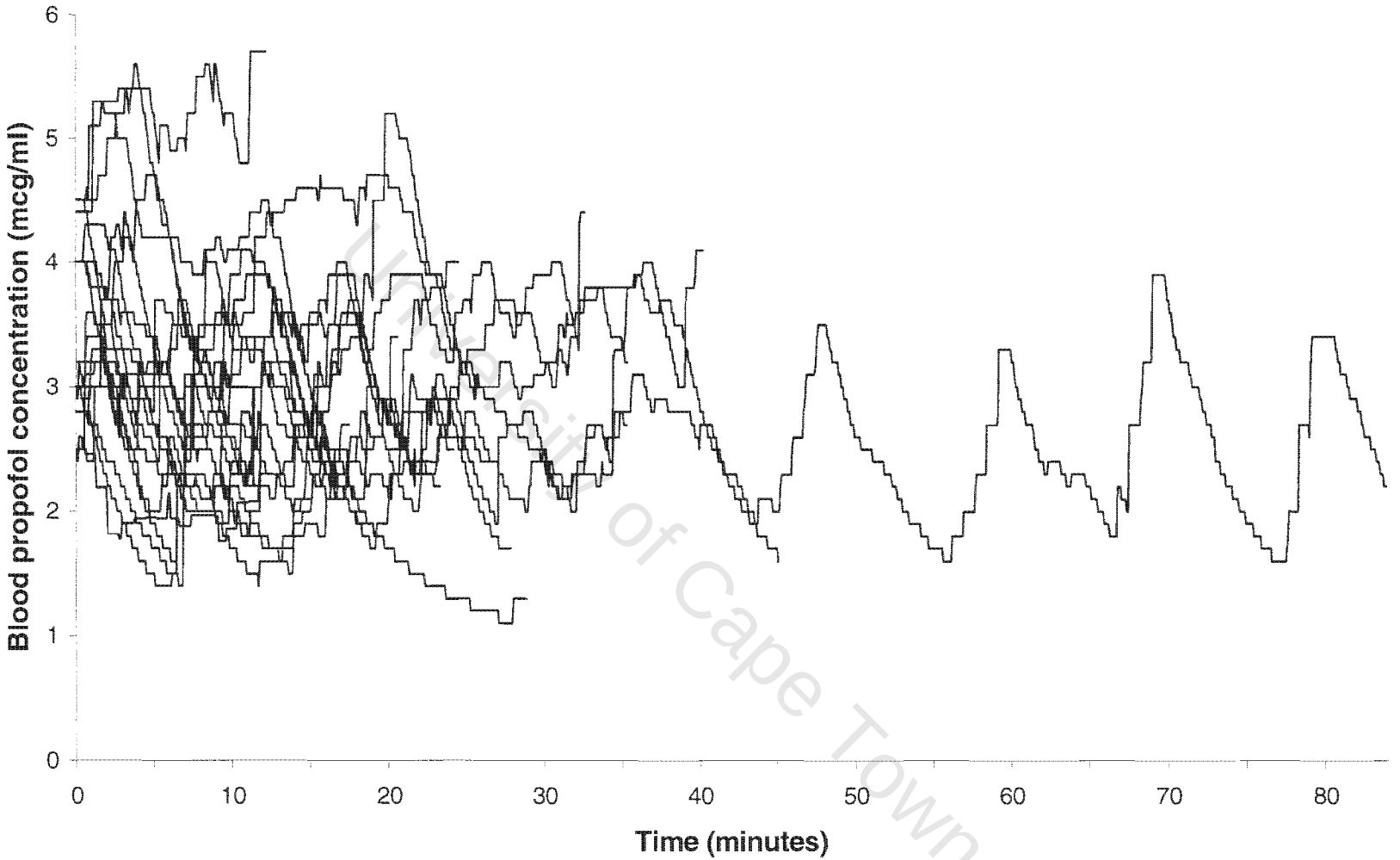


Figure 14.2: Estimated blood propofol concentrations (μg/ml) during automatic control of anaesthesia

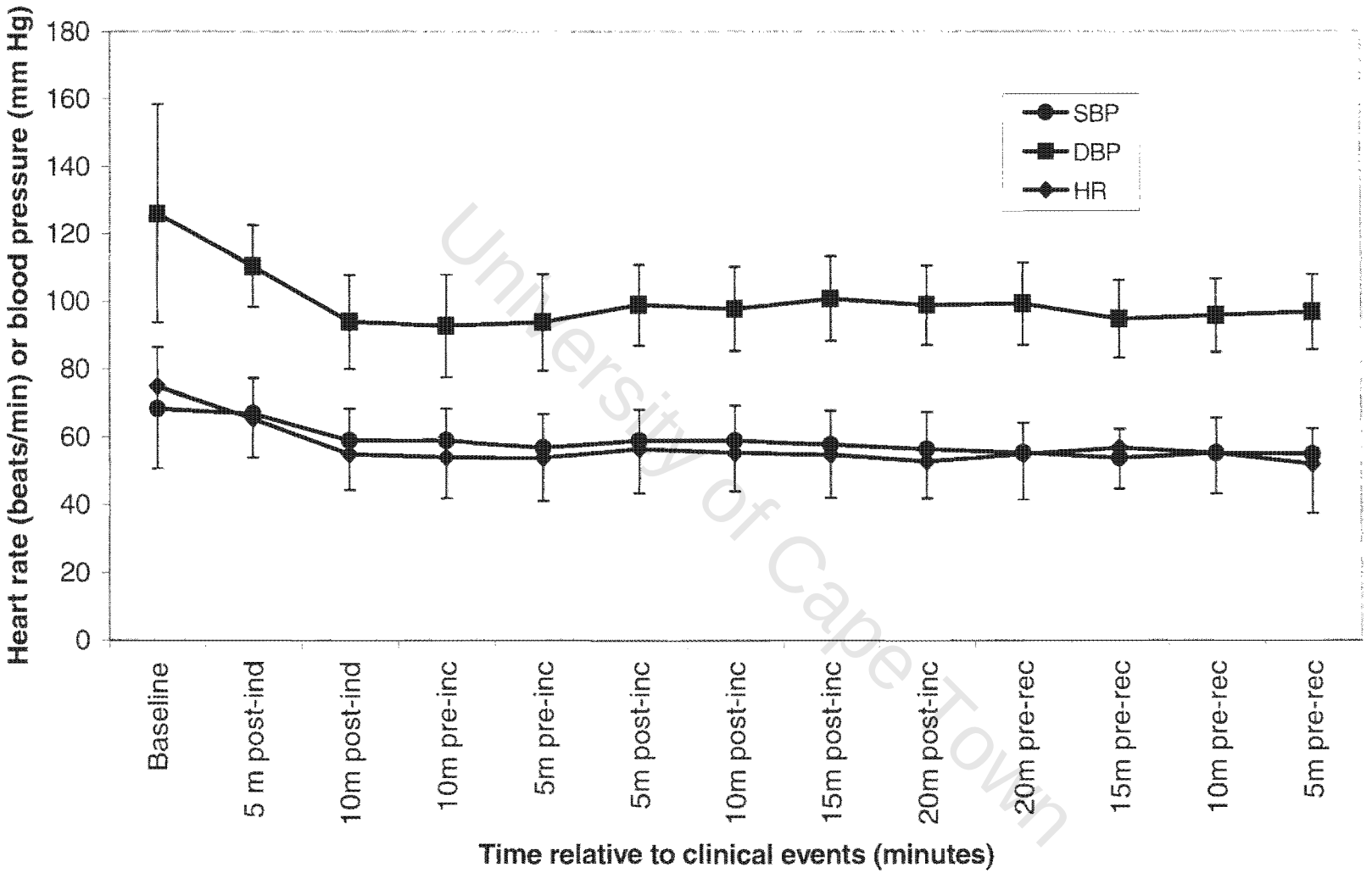


Figure 14.3: Trend in heart rate and blood pressure during the course of general anaesthesia. "ind" = induction; "inc" = incision, "rec" = recovery of consciousness. Feedback control of anaesthesia spanned the period from 5 min pre-incision until 10 min pre-recovery

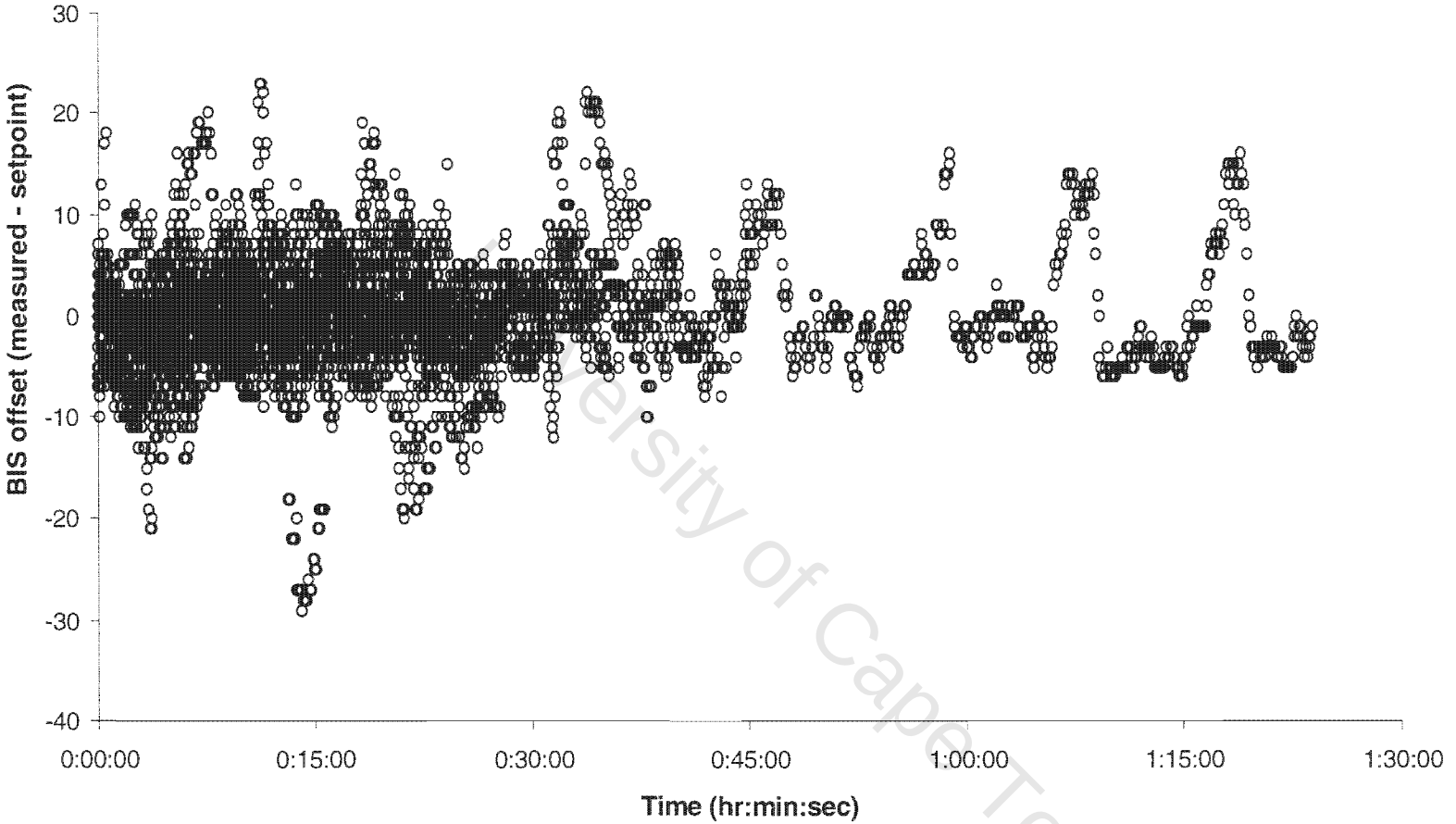


Figure 14.4: Individual offset values (measured BIS - set point) during automatic control of anaesthesia

Chapter 15

Testing and comparison of different control algorithms

Brief description of a study performed by Struys and de Smet, with which I collaborated.

BACKGROUND

Different types of control algorithms have been used for feedback control. A PID control algorithm is used in BISCLAN, and variants of this type of algorithm are commonly used to control household appliances and numerous industrial processes. In Glasgow, PID algorithms have also been used successfully for AEP-guided feedback control of anaesthesia, and for feedback control of arterial blood pressure.[166]

As discussed in previous chapters, PID algorithms have some limitations. The gain constants have to be tuned for a typical population, but do not necessarily apply to individuals. If one or more gain constants are not appropriate for an individual person or process, then instability of the control variable can arise. Adaptive algorithms try to adapt the system to suit the individual, the aim being to improve control accuracy and responsiveness while limiting the potential for instability and oscillation. , but are these theoretical benefits likely to translate into real, clinically significant benefits for patients?

BISCLAN has been tested in 3 clinical studies (chapters 13, 14 and 19), but in these and all such studies, ethical considerations have made it necessary to test the system under favourable conditions, particularly when the aim is to control *anaesthesia*, as the consequences of excessively "deep" or "light" anaesthesia can be serious. Thus during the studies of BISCLAN's performance during general anaesthesia, situations where patients were receiving effective analgesia were chosen. Of the studies in this

thesis the least favourable conditions for automatic control were present when BISCLAN was used for closed loop control of sedation during colonoscopy (chapter 19). These patients received no analgesia, so that the control system was required to deal with anxiety, and the responses to pain, with an infusion of a hypnotic with no analgesic effects.

When Struys and colleagues published the results of a study of closed loop control of anaesthesia in which patients received spinal analgesia in addition to general anaesthesia, [112] an accompanying editorial by Glass and Rampil criticised the lack of testing of current control algorithms under more "extreme" conditions.[167] In response to this criticism Struys and colleagues developed a sophisticated computer simulation process for evaluating controllers under varying conditions. They recently performed a study to test this methodology and went on to compare the control performance of a model-based adaptive algorithm with that of the PID algorithm used in BISCLAN.

METHODS

Equipment: software and hardware

The simulation process uses two computers and an infusion device. The first computer runs RUGLOOP II © (a BIS data management and closed loop anaesthesia system [#]), while the second computer runs a patient simulator. At system start-up the patient characteristics and target BIS value are supplied as inputs to the closed loop system. The closed loop system controls the infusion device (i.e. the infusion rate), but the second computer is also able to communicate with the infusion device to enable it to keep track of the drug volumes infused into the virtual patient.

[#] RUGLOOP, written by Tom De Smet, (Electronic Engineer) and Michel MRF Struys (Professor in Anaesthesia). More information at http://www.anesthesia-uzgent.be

The effects of the propofol infusion and the surgical stimuli on the BIS values from the virtual patient are calculated as follows: first the patient simulator calculates the estimated blood and effect-site propofol concentrations, and the likely effect these will have on the BIS based on an E-max pharmacodynamic model using data recorded previously from "real" patients. This BIS estimate is then delayed for a period of time to simulate processing delay before having a randomly calculated noise value (mean 0, standard deviation 3) added to it to simulate BIS variability. Finally, when surgical or clinical "events" (read from a script file) occur, they are incorporated as an offset or bias on the BIS.

The BIS values generated by the patient simulator are formatted in the same manner as the data produced by the A-2000 BIS monitor, and passed as inputs to the closed loop system, which then runs the control algorithm to determine the resulting alteration to the control actuator. RUGLOOP was programmed to be able to use either of two published controllers: a model-based adaptive control algorithm [160] or the PID algorithm [168] used in the first study of BISCLAN (Chapter 13). When the model-based algorithm was studied the output was an effect-site concentration, whereas when the PID algorithm was studied the output was a target blood concentration. RUGLOOP then calculated the propofol infusion rates required to generate the target concentration using the Schnider pharmacokinetic model.[163]

Study protocol

Ten virtual patients were studied. Each was given a different pharmacodynamic profile based on pharmacodynamic E-max models developed from a study of real patients during induction of anaesthesia.[112] A standard stimulus profile (Figure 15.1) was prepared and applied to each virtual patient during the course of six general anaesthetics

lasting 1 hour. Each patient received 3 anaesthetics controlled by the model-based controller (with set points of 30, 50 and 70 respectively) and 3 anaesthetics controlled by the PID controller (again with set points of 30, 50 and 70 respectively). Induction of anaesthesia was achieved with step-wise increases in target propofol (with the model-based controller this is part of the control algorithm). Feedback control was initiated once the BIS set point value had been reached. Performance of the two controllers was thus only analysed and compared during maintenance of anaesthesia.

Data analysis

The percentages of time that the BIS was within +/- 10 BIS units of the target value, or was above or below that range, were calculated at each target. MDPE, MDAPE, divergence and wobble were calculated using the methods recommended by Varvel et al,[155] (summarized in chapter 13). Divergence is the slope of the linear regression line of the absolute value of the PE over time – a positive value indicates that the inaccuracy is increasing over time, whereas a negative value indicates a convergence of the measured values with the target. Significance between controllers was tested using the paired t-test (SPSS 10.0, SPSS Inc., Chicago, Il, USA).

RESULTS

Although there was a tendency for the model-based controller to infuse greater total volumes of propofol at all set points than the PID controller, this difference failed to reach statistical significance. Figure 15.2 shows the trend of BIS values in a typical virtual patient. In this patient control was clearly better with the model-based controller than with the PID controller when the set point was 50 or 70.

Table 15.2 shows the percentage of maintenance time during which control was acceptable (BIS within 10 units of set point), or inadequate (BIS either 10 units above

set point of 10 units below set point). At set points of 30 and 50 control was acceptable for a significantly greater proportion of time with model-based control than with PID control. At all set point values the BIS was too high for a greater proportion of time with PID control, whereas at a set point of 70 BIS was too low for a significantly longer proportion of time with model-based control.

Control performance parameters as assessed by the Varvel criteria [155] are shown in Table 15.1. Although overall bias (MDPE) was significantly better with the PID controller than the model-based controller, inaccuracy (MDAPE) and wobble were significantly worse. Divergence figures for PID control were better than for model-based control, indicating that control performance had a greater tendency to improve during the course of the anaesthetic. For both controllers, performance parameters were best when the set point was 70 (all parameters are relative to the set point rather than absolute measures – thus the errors may be of similar magnitude at different set points).

DISCUSSION

This valuable study – the only one of its kind so far – objectively compared control performance between two published controllers: the PID control algorithm used in BISCLAN and a model-based controller used in the RUGLOOP system developed by Struys and de Smet. Control performance was tested under more severe conditions than could possibly be used with human experiments, as the stimulus profile represented severe and extreme changes in stimulus, for patients not receiving any analgesia. The results suggest that the combination of an adaptive model-based control with an effect-site targeted TCI system is associated with better control. This is intuitive since a model-based controller that "learns" the pharmacodynamic profile of an individual subject is likely to make more accurate control decisions for that patient than a

controller based on a general population. Also, effect-site targeting is likely to be associated with a more rapid and accurate change in clinical effect.

Both controllers in this study showed a negative bias – "measured" BIS values had an overall tendency to be below the set point. One reason for this is that both control actuators are asymmetric – they can administer but not remove drug. In the case of the PID controller the bias was actually very small. This does not necessarily represent better control. Indeed control precision (MDAPE) and wobble were far worse with the PID controller (Figure 15.2, Table 15.2). The bias with the PID controller was smaller because even though there was a greater spread of errors, they were more symmetrically placed around the set point and tend to cancel each other out in the calculation of the bias.

With the PID controller, increases in surgical stimulus were associated with prolonged periods when the BIS was above the set point, followed by prolonged periods when the BIS was below the set point. In contrast, with the model-based controller, increases in surgical stimulus were associated with only brief rises in the BIS (achieved by more rapid increases in blood and effect-site concentrations), and these were followed by longer periods during which the BIS was below the target and only gradually returned to the set point. The formula for calculation of the MDAPE does not take into account the direction of the errors, and thus gives an indication of the overall dispersion and magnitude of the errors, and this explains why the precision was worse with the PID controller than with the model-based controller. The symmetrical nature of the oscillations seen with the PID controller is responsible for the higher figure for wobble found with that controller.

In a clinical situation, prolonged periods when the BIS is above the set point are undesirable, as the patients will be more likely to move if not paralysed, and more likely

to regain consciousness. Ideally periods of overshoot should be limited as far as possible, and this is achieved with the model-based controller.

The primary investigators in this study were keen to only study published controllers. Thus although effect-site steering had long been incorporated in BISCLAN, and used in two clinical studies (since published), an older version of the PID algorithm not incorporating effect-site steering was used. Other limitations of this study tend to be limitations relating to the BISCLAN system. Firstly the PID controller used constants tuned for AEP-guided control, [121] for which the set point is 35. It is thus interesting that when looking at absolute rather than relative performance measures (see Table 15.1) the PID controller in the current study performed best when the target was 30. Secondly, not only were the gain constants tuned for a different control variable (AEP), they were also tuned for use with a different control actuator (a TCI system programmed with the Marsh pharmacokinetic model[43]), whereas the control actuator used in the current study incorporated a TCI system programmed with the Schnider model.[163]

Another limitation of the current study is that although the Schnider model was used with both controllers, in the case of the PID controller a blood-targeted infusion was used, whereas an effect-site targeted infusion was used with the model-based controller. After an increase in stimulus intensity effect-site targeting will result in a significantly greater increase in infusion rate (and hence dose) than with blood concentration targeting. This may explain why overshoots were much shorter with the model-based controller, whereas undershoots were of a similar duration, when compared with the PID controller. A final limitation of the current methodology is that the patient simulator and the model-based controller used the same pharmacodynamic model. Indeed the E-max models used to generate the virtual patients used real data recorded during automatic control using the same controller (RUGLOOP) that was used

in this simulation study, albeit with different processing delays and noise superadded. This may have induced some bias in favour of the model-based controller.

Both controllers showed some degree of oscillation after sudden changes in stimulus level. This is inevitable given that feedback controllers can react to changes but cannot anticipate them. The fact that the model-based controller can update its model is the likely reason though why oscillations were less severe and were shorter with model-based control.

In summary, this study has shown that the methodology developed by Struys and de Smet is valid and useful; and that model-based control allied with an effect-site targeted infusion is associated with better control performance than PID control and a blood concentration-target infusion of propofol.

Table 15.1: Percentage of maintenance time during which BIS was acceptable (within 10 BIS units of the set point), too low or too high

	Set point (BIS units)	PID control (% of total time)	Model-based control (% of total time)
Acceptable BIS (within 10 BIS units of set point)	30	58 ± 4 *	67 ± 4 *
	50	47 ± 10 *	63 ± 12 *
	70	44 ± 9	47 ± 18
BIS too low (10 units below set point)	30	17 ± 6	17 ± 7
	50	27 ± 7	31 ± 13
	70	30 ± 5 *	48 ± 20 *
BIS too high (10 units above set point)	30	24 ± 4 *	16 ± 8 *
	50	26 ± 3 *	6 ± 3 *
	70	26 ± 5 *	4 ± 3 *

* = $p < 0.05$ between both controllers

Table 15.2: Performance results

	Set point	PID controller	Model-based	P
MDPE (%)	30	-4.2 (0.7) [2]	-8.4 (0.5) [1 2]	P<0.0001
	50	-4.2 (0.5) [3]	-13.3 (0.3) [1 3]	P<0.0001
	70	-1.2 (0.4) [2 3]	-15.1 (0.2) [2 3]	P<0.0001
MDAPE (%)	30	25.7 (0.4) [1 2]	22.6 (0.3) [1 2]	P<0.0001
	50	21.7 (0.3) [1 3]	15.9 (0.2) [1]	P<0.0001
	70	16.6 (0.2) [2 3]	16.3 (0.2) [2]	P=0.3102
Divergence ($\%.min^{-1}$)	30	-0.004 (0.0004) [1 2]	0.0013 (0.0003) [1 2]	P<0.0001
	50	-0.003 (0.0002) [1]	-0.0002 (0.0002) [1 3]	P<0.0001
	70	-0.002 (0.0002) [2]	-0.0011 (0.0002) [2 3]	P<0.0261
WOBBLE (%)	30	22.9 (0.5) [1 2]	16.3 (0.4) [1 2]	P<0.0001
	50	20.8 (0.3) [1 3]	8.8 (0.2) [1 3]	P<0.0001
	70	16.5 (0.2) [2 3]	7.8 (0.2) [2 3]	P<0.0001

[1] = $p< 0.05$ between target 30 and 50

[2] = $p< 0.05$ between target 30 and 70

[3] = $p< 0.05$ between target 50 and 70

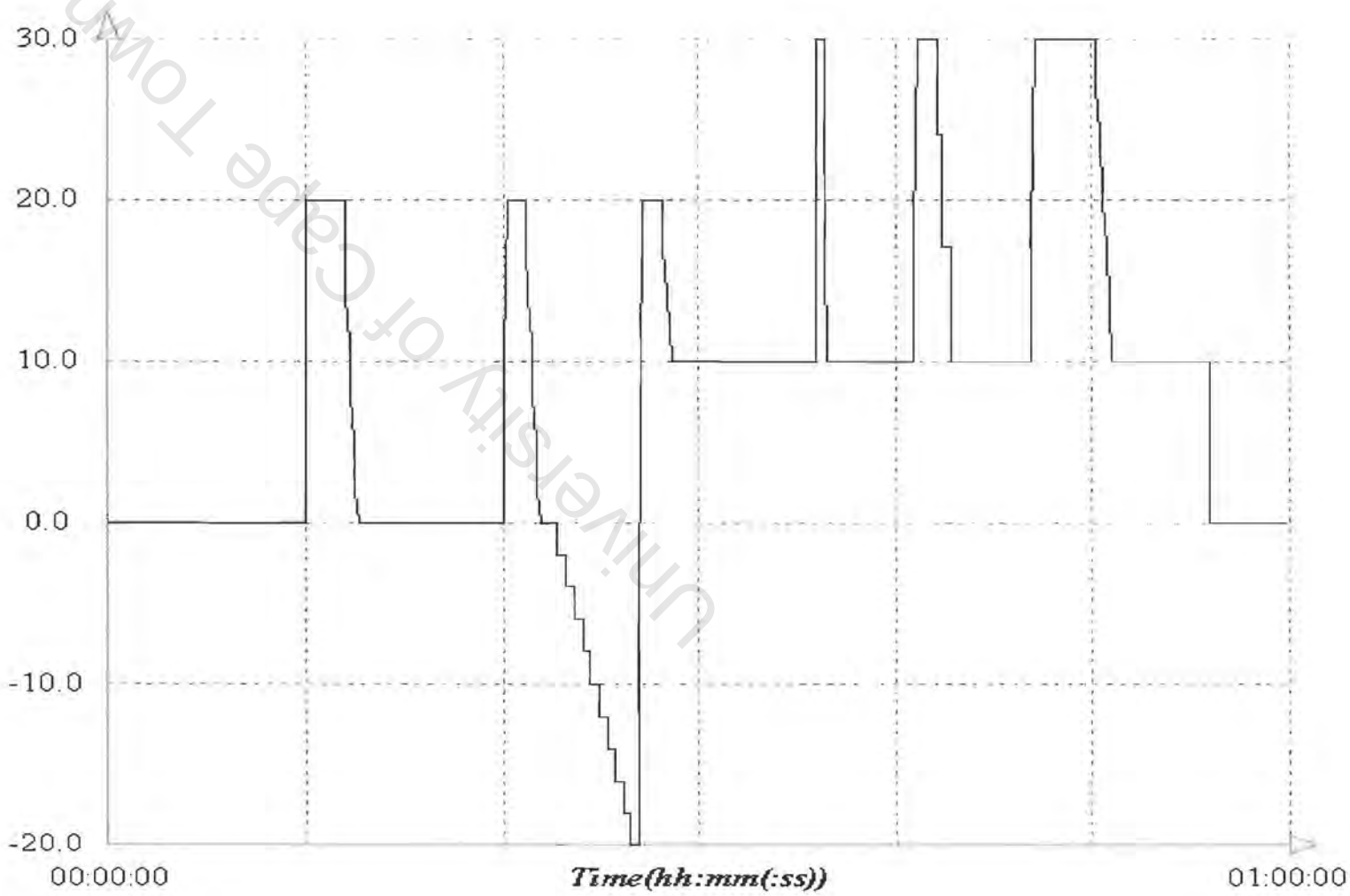
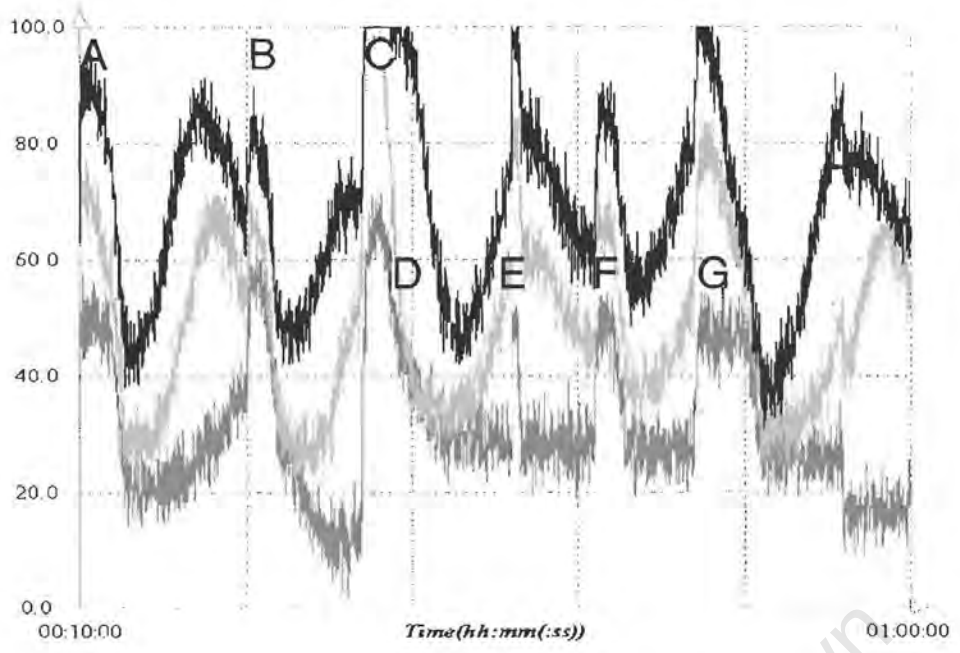
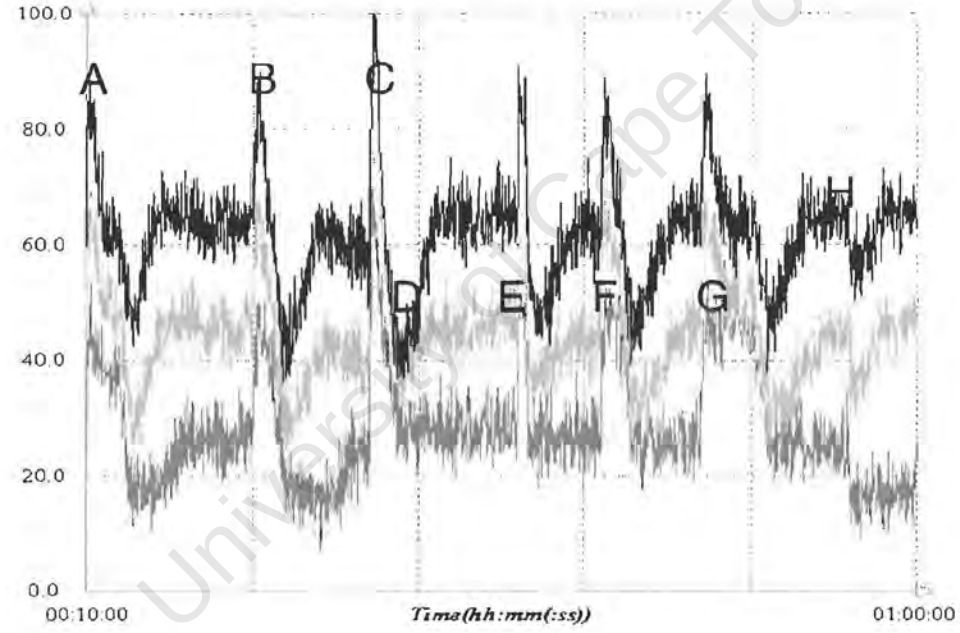


Figure 15.1: Stimulus profile applied to each virtual patient to simulate the effects of introduction and withdrawal of surgical stimuli



PID controller



Model-based controller

Figure 15.2: BIS trends for a typical "virtual patient" controlled by the PID controller (upper figure) and "model-based" controller (lower figure). Letters A to H correspond to the 7 changes in surgical stimulus shown in the profile in Figure 15.1. The differently weighted traces correspond with different set points: heavy trace = set point of 70, light trace = set point of 50, intermediate trace = set point of 50.

Closed loop control of sedation

Chapter 16

Patient-controlled sedation: rationale, literature overview

In hospitals around the world, numerous procedures are performed daily under sedation, usually in sites remote from the operating theatres, and without anaesthetic supervision. Examples of these procedures include diagnostic procedures of the upper airway (such as bronchoscopy and laryngoscopy), upper and lower gastrointestinal procedures (such endoscopies and biopsies), dental extractions and interventional radiological procedures. Typically the physician who is responsible for administering the sedative drug, or who has instructed a non-medical person to administer the drug, is also responsible for performing the operative procedure.

There are several problems with operator-administered sedation. The first is that it is difficult to concentrate on performing a procedure while also monitoring a patient for signs of adverse effects of the sedative agents (e.g. loss of consciousness, respiratory depression and loss of protective airway reflexes) The task of monitoring the patient is often delegated to a non-medically trained staff member, who may not be suitably trained in the recognition and management of these complications.

Another problem of operator-administered sedation is the choice of agent. Short-acting agents may be safer to use because the adverse-effects are of shorter duration, but unless the procedure is very short, multiple doses are required and this is distracting to the operator. Thus medium- or long-acting agents are usually used, and while these agents may be more convenient to use, when complications arise they may be fatal if not detected and treated promptly. Another issue related to choice of agent is that during a surgical procedure, a

combination of analgesia and sedation are required. Thus, more than one drugs is commonly used – typically a combination of a benzodiazepine (such as midazolam or diazepam) and an opioid (such as pethidine or fentanyl). There are several problems associated with the use of such combinations. For both benzodiazepines and opioids there is a large degree of inter-individual pharmacokinetic (PK) and pharmacodynamic (PD) variability. Similar doses administered to seemingly similar patients may result in very different blood concentrations (PK variability). PD variability in the population is huge – vastly different blood concentrations are required to achieve similar clinical effects. Moreover, when these agents are used in combination they result in PK and PD interactions – thus higher than expected blood concentrations may occur, and there will be varying degrees of synergism too, which applies to the desired and the adverse effect of the agents. It is thus difficult to predict the required doses of combinations of agents, and the likely clinical effects of combinations.

Many non-anaesthetists (and indeed many anaesthetists) favour the use of midazolam for sedation. While midazolam has some favourable PK characteristics, it has other less favourable properties, one of which is the relatively slow rate of equilibration between the blood and the effect site. After a single dose, clinical effects are apparent after 2 to 2.5 min, but computer simulations based on the model published by Zomorodi and colleagues[169] show that the peak effect only occurs at about 13 min. For short procedures the peak effect may occur after the end of the procedure, when the patient may no longer be closely monitored. To properly assess the effects of a single dose, it is necessary to wait 13 min, but this is not always practical. If, the physician administers supplementary doses after a shorter interval, the effect-site concentrations may eventually rise to levels associated with serious adverse effects.

A study of outcome following upper gastro-intestinal endoscopy, performed in two regions of England, showed a 30 day mortality of 1:2000, and a morbidity rate of 1:200.[170] There are many reasons why this figure is much higher than the mortality rate associated with general anaesthesia (~1:10,000) not least among which is the fact that the patients undergoing these procedures are often unwell to start with. To minimise the risks of sedation, it may be argued that an anaesthetist should always be present when sedative drugs are administered. Without a large expansion in the anaesthetic workforce this is not practical. In 1992 the Joint Working Party of the UK Royal College of Radiologists and UK Royal College of Anaesthetists recognised the problem of limited numbers of anaesthetists and published guidelines for sedation during radiological procedures.[103] This report endorsed the view of many anaesthetists that it is safer to use a single drug for sedation, rather than a combination of drugs, and that the goal of sedation should be to achieve a state of "conscious sedation" during which the patient is able to respond to verbal command. Despite these recommendations, the findings of the study of outcome after endoscopy in England [170] and the recommendations of a UK endoscopy working party,[171] it remains common practise for UK radiologists and endoscopists to administer benzodiazepine and opioid combinations.

When an anaesthetist is present, his knowledge and skills should make sedation safer. It does not necessarily follow that anaesthetists are better than other health care professionals at assessing the degree of anxiety or distress suffered by patients. Assessment of anxiety, an emotion or feeling, is very difficult, even when the distress suffered is constant.[111] During the course of a surgical procedure the surgical stimulus will often change with time, so that the dose of drug required changes with time.

Two possible solutions for this problem of assessment of sedation and anxiety exist, and were explored as part of this thesis. Both employ a form of feedback control.

The first is to allow the patient to self-administer the sedative agent, and the second is computerised closed loop control guided by an automated, objective measure of depth of sedation, such as the BIS.

Patient-controlled analgesia (PCA) systems have become popular in recent years. A patient using a PCA system is in effect a closed loop system. The control variable is the subjective experience of pain, which is influenced by the nature and severity of external disturbances and stimuli, and by the psychological and physiological make-up of the patient. The set point is determined by the balance of the patients' tolerance of pain and of the adverse effects of the analgesic. In this case, the control actuator is the analgesic infusion pump, and the dose delivered depends on the control algorithm (bolus dose and lockout period), set point, internal and external noxious stimuli, and the patients' individual PD and PK profile. PCA systems thus enable the patient to self-administer an individually tailored dosing schedule, potentially improving patient satisfaction. At the same time, by incorporating a feedback element, there is the potential for improved safety (as the sedative effect of commonly used analgesic agents will prevent excessive use of the system).

PCA technology has been applied to enable patient control of sedative administration, with the aim of improving safety and patient satisfaction. In the context of patient control of sedation, the safety benefit of the feedback system relies on the fact that patient will be unable to activate the handset when deeply sedated, and the appropriateness of the algorithm. The lockout should be sufficiently long to allow equilibration between the blood and effect site concentrations before another dose is allowed, and the dose or increment applied should be small enough to maintain safety, but also sufficiently large to generate a significant change in sedation status.

One of the first systems, developed by Loper, enabled patients to self-administer bolus doses of midazolam for sedation during mechanical ventilation.[172] Although the lockout period (8 min) was not long enough to allow blood-brain equilibration, this was counteracted by the fact that the bolus size was kept small (0.25mg). With these settings use of the system resulted in reduced anxiety scores and reduced morphine requirements. The system was effective for long-term sedation, but is unlikely to be effective or practical for short-term sedation of healthy patients as it will take at least 32 min for a patient to self-administer 5mg!

Propofol's pharmacokinetics (short onset and duration of action), combined with the pleasant sedative and anxiolytic effects, make it more suitable for patient-controlled sedation than midazolam. In the early 1990's Rudkin and colleagues performed a series of studies of patient-controlled administration of propofol for third molar extractions (local anaesthesia was also used). In their first study bolus doses of propofol (0.7mg/kg, lockout 1 min) were found to be safe, and associated with high levels of patient satisfaction.[173] In another study patient-controlled propofol was compared with anaesthetist-administered midazolam and fentanyl, and was found to be associated with improved patient satisfaction and lighter levels of sedation.[174] Later they compared patient controlled administration of propofol (20mg boluses, 1 min lockout) with patient-controlled administration of midazolam (0.5mg boluses, 1 min lockout).[175] In the latter study, patient satisfaction was similar between the two groups, but propofol was deemed to be the safer choice of agent because it caused less impairment of post-operative cognitive function. Finally they performed a cross-over study to compare propofol infusions (3.6 mg/kg/hr) with patient-controlled propofol boluses (18 mg over 5.4 sec, 1 min lockout) – safety outcomes were similar between the two methods, but patients expressed a strong preference for patient control.[176]

Although Rudkin and colleagues demonstrated good safety with patient-controlled bolus propofol administration in their studies, it should be noted that only modest numbers of button presses were made! If for example during the cross-over study, [176] an anxious patient had pressed the control button continuously, the patient would have self-administered propofol at an average rate of 18 mg per 65.4 sec – this is equivalent to a rate of 990mg/hr. For a patient weighing 70 kg the rate of propofol administration (14.1 mg/kg/hr) will result in a blood propofol concentration of 3.8 µg/ml after 10 min, and of 5.0 µg/ml after 30 min. (TIVATrainer, F. Engbers, Leiden) Given that the Cp50 for loss of response to painful stimuli with propofol is of the order of 6 µg/ml,[39;41] these concentrations are likely to result in loss of consciousness. It is interesting that with consecutive studies, Rudkin and colleagues progressing decreased the bolus dose size. This may have been because of safety concerns

A significant problem with repeated bolus dose administration is it results in large swings in blood concentration. When large bolus doses are used it is possible that patients will vacillate between oversedation, with potential adverse effects, and undersedation, with poor patient cooperation and satisfaction. One potential solution is to have a system where patient control results in short infusions, or infusions at increasing rates. Both strategies have limitations – infusions of propofol only produce steady state blood concentrations after approximately 2 hours.

A better solution is to combine target-controlled infusion (TCI) technology and patient control, to enable patient-maintained sedation (PMS). As discussed earlier, TCI systems, deliver almost step-wise changes in blood drug concentration, and thus offer the potential for more stable and satisfactory provision of sedation. PMS systems allow the patient to titrate the sedative blood concentration to the precise level they require.

A propofol PMS system was developed in Glasgow during the mid-1990's. It consists of the same TCI system described in chapter 9, but with a patient control handset connected to the Graseby controller. When the handset is connected to the controller, the controller automatically recognises this and switches to patient-control mode. The handset itself is a mechanical device. It has a button, which when depressed, causes a pressure wave to travel down a plastic tube that connects to a pressure-sensing device inside the controller. In patient control mode the anaesthetist must enter the following parameters: patient age and weight, initial blood propofol concentration, increment in blood concentration following patient activation and lockout period. For the patient to successfully alter the target blood concentration outside of the lockout period are required two consecutive presses of the handset button within 1 sec. If a validated press occurs the target blood propofol concentration is increased by the preset increment. To achieve this, as with any TCI system, the system will first administer a rapid infusion to increase the blood propofol concentration in the central compartment to the new concentration, and then administer a stepwise decreasing rate infusion to compensate for losses of propofol from the central compartment by redistribution and metabolism. If no validated presses occur, the system initially keeps the target propofol concentration unchanged, but if after 6 min no further presses have occurred it will reduce the target concentration by the incremental amount.

In an early study 39 patients used the system to self-administer propofol for sedation during orthopaedic surgery under local or regional anaesthesia. [110] The initial concentration was 1 µg/ml, the increment 0.2 µg/ml and the lockout 2 min. Patients administered a median blood propofol concentration of 0.8 – 0.9 µg/ml (i.e. lower than the starting concentration). The mean infusion rate was 2.4 (range 0.18 – 7.9) mg/kg/hr. No patient lost consciousness, but 8 patients required supplementary oxygen after a

period of arterial oxygen desaturation. There was a high level of patient satisfaction. In another study the same system, with the same settings, was used to provide 45 min of "premedication" for 20 patients awaiting day case surgery.[177] Median target propofol concentrations at 15, 30 and 45 min varied between 1.0 and 1.3 μg/ml, and mean propofol infusion rate was 3 mg/kg/hr. There were significant reductions in VAS and STAI (Spielberger state trait inventory) anxiety scores, and no episodes of cardiovascular instability or excessive sedation (all continued to respond to voice). However, 2 patients required supplementary oxygen because of desaturation. Patient satisfaction was very high – most patients reported the premedication as excellent, and better than previous experiences of oral premedication.

The aim of our team in Glasgow was to produce a PMS system that could be used without anaesthetic supervision. Using the same settings as before, Murdoch studied the safety of the system in 10 volunteers who were encouraged to operate the system repetitively in an attempt to anaesthetise themselves. [178] The median target propofol concentration was 2.0 (range 1.4 to 3) μg/ml, and the mean propofol infusion rate was 5.3 mg/kg/hr – the safety limits of the system were thus subjected to greater "stress" than in previous studies. Two patients became oversedated (one did not respond to painful stimuli), indicating that further refinements were required before the system could be recommended for use without anaesthetic supervision. I thus performed two further studies of PMS – one using revised system settings, and another using an effect-site targeted (as opposed to a blood concentration targeted) PMS system.

The other solution to the problems associated with assessment of anxiety by an outside observer, is to use an objective measure of sedation such as the BIS to guide a computer-controlled infusion of a sedative agents. Thus, in a further, final, study, the

use of BISCLAN for automatic feedback of propofol sedation during colonoscopy was evaluated.

Chapter 17

Project 6: **Safety of patient-controlled sedation using a revised blood-targeted TCI system**

BACKGROUND AND AIM

As mentioned in the chapter 16, patient-controlled sedation is associated with greater patient satisfaction than anaesthetist-administered sedation, but existing systems are not sufficiently safe to recommend for use without anaesthetic supervision.

Patient-maintained sedation (PMS) is a sophisticated means of enabling patients to self-administer a target-controlled infusion. The PMS system developed in Glasgow was discussed in chapter 16. In previous studies 2 patients using the system developed respiratory depression (causing oxygen desaturation)[177] and 2 volunteers lost consciousness.[178] This was because the lockout period of 2 min was too short to allow equilibration between the blood and effect-site propofol concentrations (Figure 17.1). Thus, as the subjects repeatedly pressed the button, the blood propofol concentration was repeatedly increased prior to equilibration, allowing the gap between blood and effect-site concentration to grow. When the effect-site propofol concentration eventually reached a threshold sufficient to cause deep sedation, the volunteer forgot to or did not care to press the button any longer. For the next 6 min the blood propofol concentration was kept constant, allowing the effect-site concentration to rise further. In two subjects the effect-site concentration rose above the threshold required for loss of consciousness.

Our overall goal was to improve the safety of PMS. The aim of this study was to determine if a revision of the PMS system settings improved safety. As a secondary aim

we also wanted to attempt to quantify the relationship between propofol concentration, BIS and loss of memory in the subjects studied.

The reasoning for the changes to the PMS settings was as follows. After a change in the target blood propofol concentration it takes at least 10 min before there is complete equilibration between blood and brain concentrations. A lockout period of this magnitude is impractical in a busy clinical setting, where some patients will require several increments before adequate sedative concentrations are achieved. Thus it seemed that the logical next step would be to try using a smaller increment. A lockout time of 4 min was chosen – a compromise between speed and safety. It was also recognised that the initial concentration setting of 1 µg/ml was probably too high, given that the median target propofol concentration "chosen" by the patients in one of the PMS studies was between 0.8 and 0.9 µg/ml. [110] The effect of these changes, a reduction of the time-lag between the blood and brain propofol concentrations, is illustrated in Figure 17.2. These settings reduce the gap between blood and effect-site concentrations, thereby improving safety, but they do cause the system to take longer to reach any given concentration above the initial concentration.

METHODS

Local Ethics Committee approval was obtained for this study. Twenty healthy adult volunteers, aged 24-46 yr, were enrolled. To be considered for inclusion they had to be ASA status I or II. Exclusion criteria were a history of use or abuse of sedative or psychoactive agents, and allergy to propofol or its constituents. All volunteers gave informed consent.

As described previously, the PMS system consists of a Graseby 3400 pump connected via RS232 ports to a Graseby pump controller containing a microprocessor

programmed with the Marsh adult pharmacokinetic dataset.[43] The microprocessor calculates the infusion rates required moment-by-moment and transmits these to the infusion pump. It also calculates and displays the estimated effect site concentration.[179]

The subjects fasted for 6 hours. Before starting the study they were shown how to use the control button, and asked to try to deliberately induce loss of consciousness using the system. Venous access was secured and routine monitoring commenced and continued throughout the study (non-invasive arterial pressure, pulse oximetry and ECG). The propofol infusion was started with the initial target concentration (C_T) set to 0.5 μg ml^{-1}. Once the effect-site concentration was at least 0.4 μg ml^{-1} (80% of the blood concentration) the patient control handset was activated. Thereafter the subject was able to increase the propofol C_T in increments of 0.1μg ml^{-1} by clicking the control button twice within 1 s. The lockout period, before a further target increase could occur, was 4 min, and the maximum possible C_T was 3μg ml^{-1}. To assess the effects of propofol on memory subjects were given a keyword to remember every 15 min.

Non-invasive arterial pressure, respiratory rate, oxygen saturation and a modified Steward sedation score[109;110] were recorded manually every 5 min. Subjects were observed continuously for signs of airway obstruction (such as paradoxical chest wall movement). Supplementary oxygen by facemask was administered if the Spo_2 was < 94% or the respiratory rate <8. Subjects were attached to an A-1000 BIS monitor and BIS values were recorded electronically. If subjects failed to press the activating device for 5 min but were still alert, they were given one further reminder. When the subject became too sedated to press the button or the maximum C_T was reached, the infusion was discontinued, and he or she was observed until fully alert and able to walk unaided. Once able to walk, subjects were tested for spontaneous recall of keywords.

Statistical analysis

Volunteer characteristics and propofol concentration data are presented as median (range). Binary logistic regression was used to determine the significance of the correlation between propofol concentration and memory; and to determine the effect-site propofol concentration associated with 50% loss of memory for words (C_e50).

RESULTS

Volunteer characteristics and main results are summarised in Table 17.1.

All subjects reached a state in which they were too sedated to remember to press the button, but all remained responsive to verbal command throughout the study period. The median Steward score when subjects stopped pressing the button was 7 (range 7 – 9) and the minimum score of any subject at any time was 7. The median blood propofol concentration at maximal sedation was 1.7 (range 1 – 2.5) $\mu g\ ml^{-1}$ and the median time taken for this to occur was 65 (30 – 110) min. Median interval between stopping the infusion and mobilisation was 12 (7 – 22) min.

No volunteer had a decrease of more than 10% from baseline of HR or mean NIBP. Airway control was maintained in all subjects, but one subject had a brief period of apnoea at a blood propofol concentration of $1.0\mu g.ml^{-1}$ associated with a decrease in SpO2 to 85%. On being told to take a breath he responded: "What, have I desaturated?" whereupon his SpO2 rapidly increased and remained >94%. All other subjects had SpO2 ≥ 93% throughout the study and did not require or receive supplementary oxygen.

BIS data were recorded but were not backed up at the time of a subsequent hard disk failure that corrupted the files. Electronic files of BIS data from 4 volunteers were recoverable, and in one case a manual record of the BIS values at 5 min intervals was found. BIS data are thus only available for 5 volunteers, and are shown in Figure 17.3.

One of the 5 volunteers remained conscious despite having BIS values between 55 and 60.

There was a significant correlation between effect site propofol concentration (C_e) and memory ($P < 0.001$, -2 log likelihood 85.4). The logistic regression equation for the effect-site propofol concentration was:

$$\text{Ln (Odds of loss memory for words)} = -3.172 + 2.754 \times C_e.$$

The overall odds ratio for propofol concentration having an effect on memory (i.e. $e^{2.754}$) was 15.7 (95% confidence interval 3.3 – 73.8). The effect-site propofol concentration associated with 50% loss of memory for words was 1.23 $\mu g.ml^{-1}$.

DISCUSSION

As mentioned earlier it was our goal to develop a patient-controlled sedation system that provides optimal sedation without requiring anaesthetic supervision. Thus any episode of loss of consciousness, loss of airway reflexes or respiratory depression is unacceptable. In this study we tested the safety of a PMS system using the minimal possible increment size, and a lockout period that we considered to be the maximum practical possible in a clinical setting.

When using this modified PMS system, 20 volunteers were able to sedate themselves, but were unable to deliberately induce unconsciousness, and quickly returned to a fully alert state. This was an improvement compared to the previous settings, which when stressed in the same way in a previous study allowed two subjects to become oversedated at a blood concentration of 1.4 $\mu g\ ml^{-1}$.[178] Our suspicion that the starting target concentration of 1.0 $\mu g\ ml^{-1}$ used in that study was too high was confirmed in the current study when one subject reached maximal sedation at a blood propofol concentration of 1.0 $\mu g.ml^{-1}$.

The altered system settings used in the current study served to reduce the lag in equilibration between blood and effect-site concentrations, but this came at a cost – maximal sedation took a long time to achieve. In the present study the median (range) time to maximal sedation was 65 (30 – 110) min compared with 29.5 (9 – 46) min with the previous settings used in that study. In stressed patients, who might require even higher propofol concentrations, this delay may be even longer, and this is unlikely to be acceptable to patients, operators and hospital managers.

Although the changes to the system settings were able to prevent loss of consciousness in the volunteers studied they were not sufficient to prevent an episode of apnoea in one volunteer. It is likely that this problem was also caused by the time lag between blood and brain concentrations, resulting in the effect-site concentration continuing to rise after the sedative threshold was passed, and rising above the threshold required for respiratory depression. With the possible exception of ketamine, all currently available hypnotics, and all opioid analgesics possessing μ agonist effects, are associated with a dose-related risk of respiratory depression. With increasing doses, the ventilatory responses to hypoxia and hypercarbia are gradually lost, and if consciousness is lost, respiratory depression may rapidly proceed to apnoea. When combinations of opioids and hypnotics are used, profound syngergism occurs, so that seemingly low concentrations can be associated with marked respiratory depression.[180,181] Safety of computerised systems may be enhanced by programming them to communicate with respiratory rate and oxygen saturation monitors; and to use such data to limit or reduce target drug concentrations.

Other than by increasing the lockout period to > 10 min, the only other possible method of reducing the delay in equilibration between target blood and brain concentrations is to employ a method that manipulates or steers the effect-site propofol

concentration, by "overshooting" the blood concentration briefly, but without allowing a significant difference between blood and effect-site concentrations at the end of the lockout period.

One such method is effect-site targeting, in which the blood concentration is manipulated to achieve as close to as is possible step-wise increases in the effect-site concentration. Toward the end of the current study we were able to access an effect-site targeted TCI system, and a study of that system is the subject of chapter 18.

The calculated propofol concentration suppressing learning (memory for words) by 50% in the current study was 1.2 µg/ml. This is somewhat higher than that found in other studies – for example, using a Trivial Pursuit question task, Leslie and colleagues found a measured Cp50 of 0.66 µg/ml,[151] while Glass and colleagues found a measured Cp50 for loss of memory for words or pictures with propofol 0.43 µg/ml.[134] The possible reasons for these differences include methodological issues (for example the way we tested for memory was not as rigorous as that used by Leslie), the fact that in our study calculated propofol concentrations were used, and these concentrations may not have been achieved, and finally differences between the intelligence and memory capacity of the subjects in the different studies.

This study has shown improved safety in a controlled, artificial environment, in non-stressed volunteers, who tried their best to stress the limits of the system. It is likely that these benefits will translate into improved safety in patient controlled sedation, but formal studies in patients are required to properly test this hypothesis.

In conclusion, the modified patient-maintained system showed better safety performance than the original prototype during volunteer testing, but failed to prevent apnoea in one subject, and could not be recommended for use without anaesthetic supervision. We also concluded that incorporation of effect-site targeting into the TCI

system might enhance safety. Finally some volunteers were conscious (responding to voice) at BIS values between 56 and 60, from which it can be concluded that when the BIS is used to guide surgical anaesthesia, the target BIS value should be less than 55.

Table 17.1. Patient characteristics and main results

Age, years	32 (24-46)
Gender, n, male:female	14:6
Weight, kg	69 (58-104)
Time to maximal sedation, min	65 (30 – 110)
Maximum blood propofol concentration ($\mu g.ml^{-1}$)	1.7 (1 – 2.5)
Minimum Steward score	7 (7 – 9)
Time between study end and mobilisation, min	12 (7 – 22)

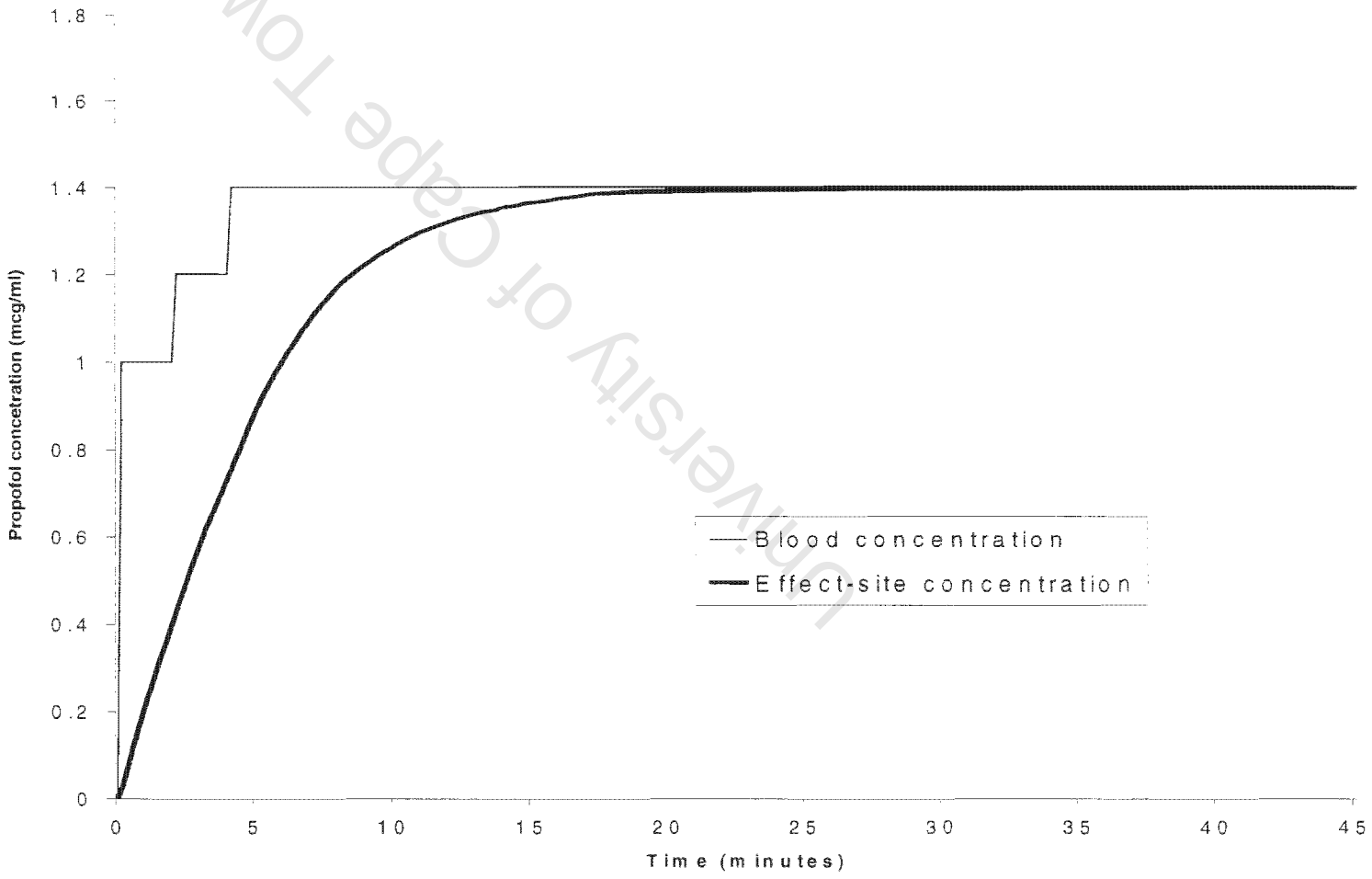


Figure 17.1: Graph of propofol concentrations that result if a subject continually presses the activating button of a PMS system with an increment of 0.2 µg/ml and lockout of 2 min. When the effect-site concentration is sufficient for deep sedation the subject will stop pressing the button. If, as in this example, this occurs when the effect-site concentration is 0.8µg/ml, the system will maintain the current blood concentration of 1.2 µg/ml, and the effect-site concentration will rise to this level, possibly leading to for loss of consciousness

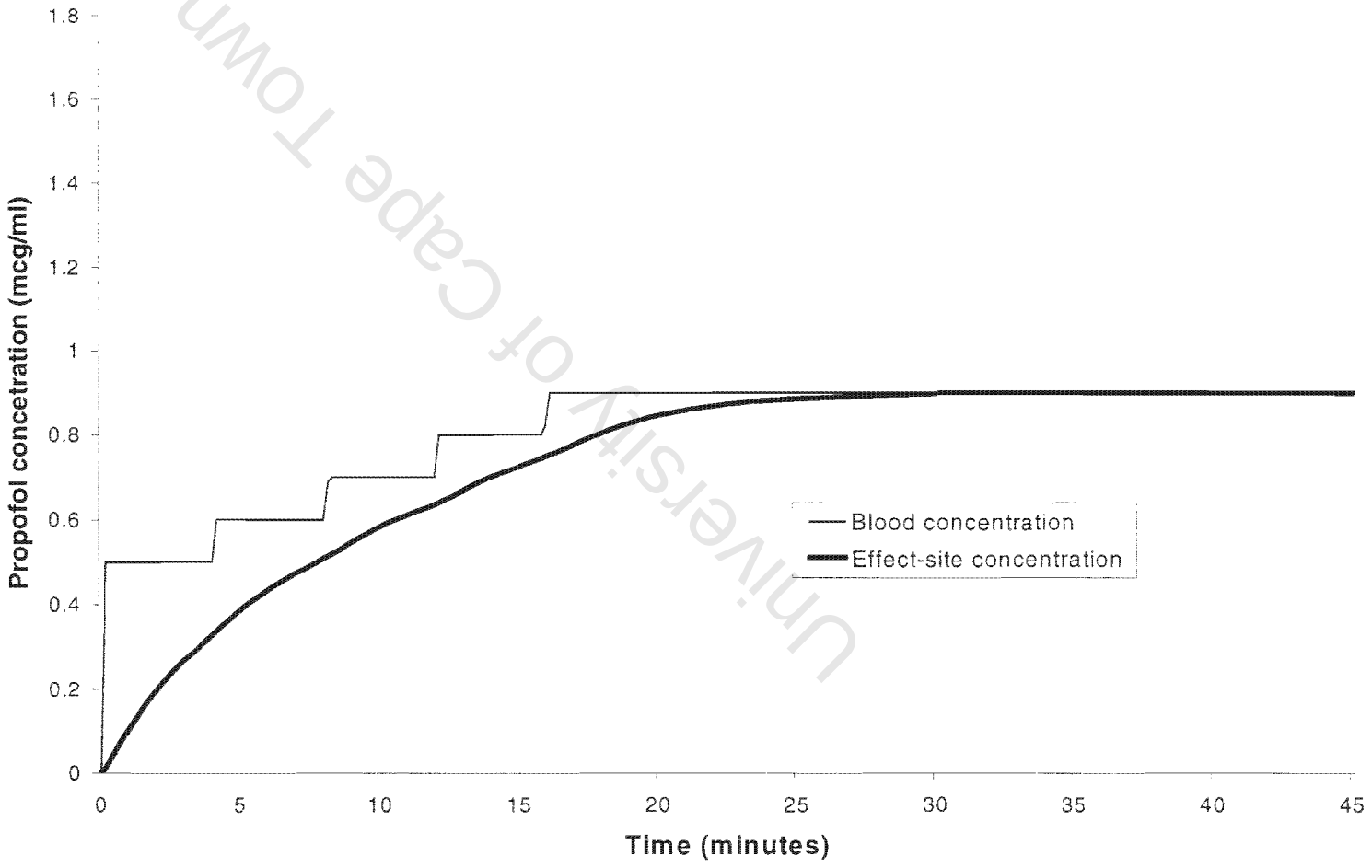


Figure 17.2: Graphic showing benefit of reduced lag between the blood and effect-site propofol concentrations if the increment size is reduced to 0.1 µg/ml, the lockout increased to 4 min and the initial concentration reduced to 0.5 µg/ml. If as in the previous illustration the patient or volunteer continuously presses the activating button of the PMS system until the effect-site concentration reaches 0.8µg/ml, the blood concentration will be maintained at 0.9 µg/ml, and the effect-site concentration will end up at 0.9 µg/ml – a smaller overshoot.

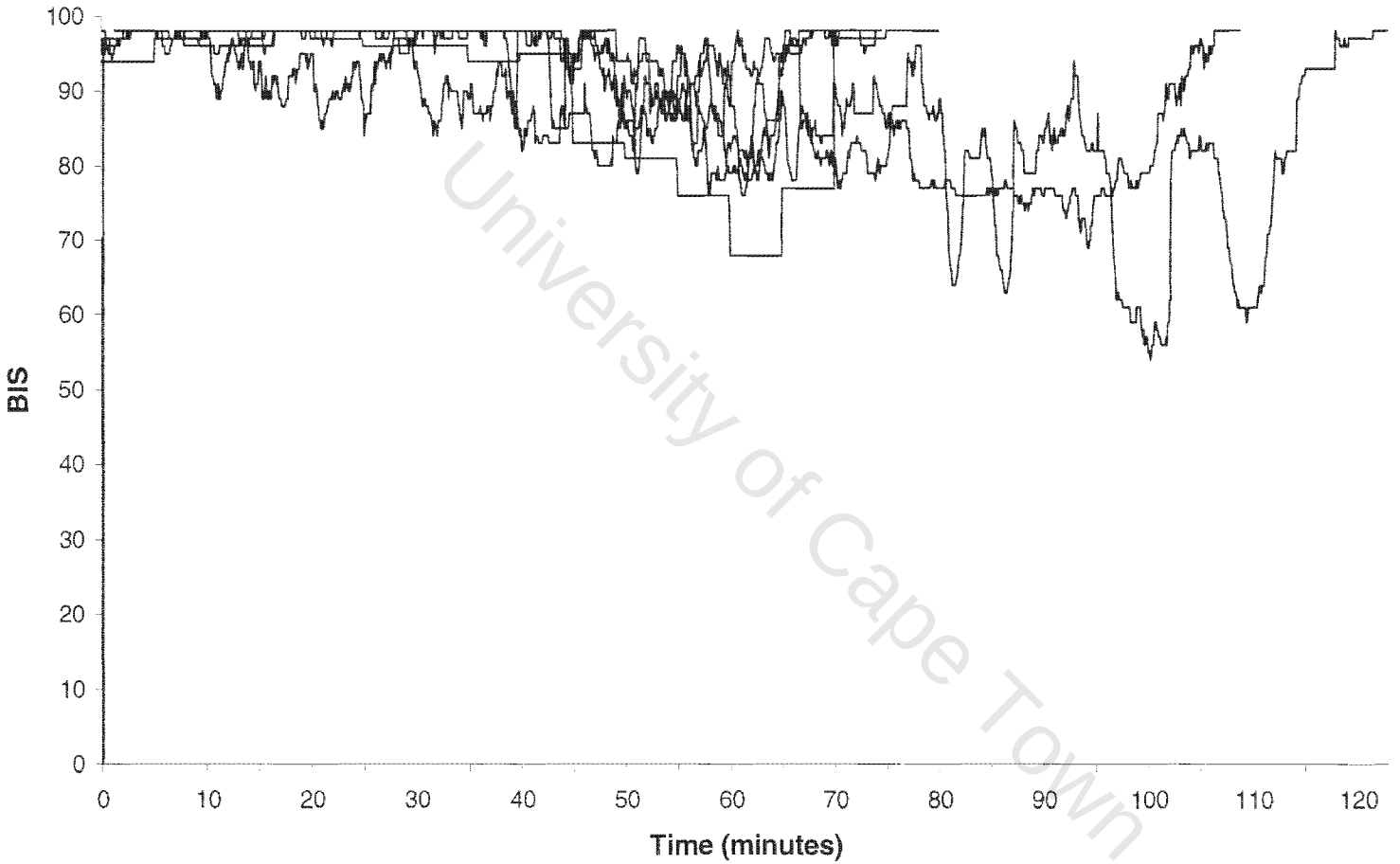


Figure 17.3: BIS data from 5 conscious volunteers during the course of PMS (data shown were recorded electronically every 5 sec for 4 volunteers, for the 5th the data were manually recorded every 5 min). Each line represents the data from 1 subject.

Chapter 18

Project 7: **Safety of patient-controlled sedation using an effect-site targeted TCI system**

BACKGROUND

During the previous study it became apparent that with propofol PMS provided by a *blood concentration* targeted TCI system, there has to be a trade-off between safety and practicality – maximal safety can only be achieved with settings that will result in long delays before patients are likely to be sufficiently sedated for surgical procedures – i.e. the smallest possible increment size, and a lockout > 10min. A "faster" system that allows a more rapid increase in blood propofol concentrations will always be less safe.

Whenever the subject stops pressing the button of a blood targeted PMS system, the system will maintain the current blood concentration. If at this time there is a large difference between the blood and effect-site concentrations (as will happen if the lockout is much less than 10 min and the subject presses the button frequently), the effect-site concentration will increase toward that blood concentration and may rise above the threshold concentration required for loss of consciousness or respiratory depression.

To fulfil our goal of a system sufficiently safe for use without the presence of an anaesthetist (or someone skilled at airway management and care of the unconscious patient) it was necessary to find a method of providing rapid increases in target concentration but without allowing large differences between blood and effect-site concentration to develop. One potential solution is to use an effect-site targeted TCI system. Indeed effect-site targeted drug therapy is inherently more logical than blood

targeting, since the concentration at the site of action of a drug is more relevant than the blood concentration.

With blood targeting the system aims to deliver a specified blood concentration – the effect-site concentration achieved depends on the blood concentration profile, the rate of equilibration between blood and brain and the passage of time. With effect-site targeting the goal is a specific effect-site concentration, achieved by manipulation of the blood concentration. This is illustrated in Figure 18.1. When the target is increased the system increases the blood concentration to an optimal level above the effect-site target. Once the blood concentration has reached this level, the infusion is switched off, so that the blood concentration decreases as rapidly as possible by re-distribution and metabolism. During this time there is a large, but temporary, gradient between the blood and effect-site concentrations so that the effect-site concentration rises exponentially (i.e. the rate of rise is proportional to the gradient).

The optimal peak blood concentration is one that, once reached, will result in the decreasing blood concentration to coincide with the increasing effect-site concentration exactly at the target concentration. Immediately this happens the infusion is re-started to maintain the blood concentration (and hence the effect-site concentration) at the target concentration. After an increase in target, it takes approximately 3 minutes for the blood and brain concentrations to converge on the target.

When an effect-site targeted TCI system is used in a PMS system, it is probably not necessary to wait the full 3 minutes for the effect-site concentration to reach a new target. Within 1 min of a change in target concentration the effect-site concentration should have increased by at least 60% of the desired increment, and within 2 min it should have increased by >90% of the desired increment. Computer simulations performed using the TIVATrainer pharmacokinetic simulator (F. Engbers, Leiden,

Netherlands) confirmed that with an increment of 0.1 µg/ml and a lockout period of 1 min, even if a volunteer or patient pressed the control button continuously, the gap between target and achieved (estimated) effect-site concentration would remain relatively small. The result of such a simulation is shown in figure 15.2. From this figure it can be seen that if just before the end of any lockout period, the effect-site concentration is just below the threshold for adequate sedation, and the subject presses the button again, the subsequent effect-site concentration is unlikely to rise above that threshold concentration by much more than 0.1 µg/ml.

The aim of the study was thus to determine if the incorporation of effect-site targeting in the PMS system, using the above settings, improved safety in volunteers. Secondary aims were to determine the relationships among BIS, blood and effect-site propofol concentrations and memory during sedation.

METHODS

The local Ethics Committee approved the study. Sixteen healthy (ASA status I) adult volunteers gave informed consent and were enrolled in the study. None had a history of psychiatric disease, use of psychoactive medications or illicit drug or alcohol abuse.

At the time of the study the PMS system developed in-house in Glasgow did not have the facility for effect-site targeted PMS. We thus used an effect-site targeted TCI system developed by Dr Frank Engbers (Leiden University Medical Centre, Netherlands). The system consists of a Fresenius Vial Master TIVA™ infusion pump (Fresenius, France) controlled by a Psion 3a™ personal organiser (Psion Inc, Concord, USA) via a RS232 serial communication port. The system software was custom-written by Dr Engbers in OPL, a programming language specifically developed for the Psion series of personal organisers. The software controls the appearance of the user interface

(on the screen of the personal organiser), implements the Marsh pharmacokinetic model [43] and controls communication between the personal organiser and the infusion pump. When the user changes the desired effect-site propofol concentration, the program calculates the optimal peak blood propofol concentration required to achieve the new effect-site target as rapidly as possible without any effect-site concentration overshoot, using an iteration process. The required infusion rates are then calculated and transmitted to the infusion pump.

At the time we had no means of direct patient control of the target concentration via the personal organiser. Changes to the target concentration were thus made manually via the keyboard of the personal organiser. To time the lockout period correctly we used one of the blood-targeted PMS systems developed in Glasgow – the PMS system was started up, but was loaded with an empty syringe not connected to the patient. The volunteer was given the handset and asked to press the button as often as possible with the aim of rendering himself unconscious. The PMS system emits an audible "peep" tone when a valid handset button press (twice within 1 sec, outside of the lockout period) is executed. Manual timing was also performed to ensure the accuracy of the lockout period.

Baseline physiologic measurements (heart rate, blood pressure, and oxygen saturation) were made and recorded before starting, and every 5 mins thereafter. Subjects were connected to an A-2000 BIS monitor (software version 3.2 or 3.3). The responsiveness portion of the OAA/S score,[107] BIS, and the target and estimated effect site and blood concentrations were recorded manually every minute. For 14 subjects the BIS was also recorded electronically. Subjects were given words to remember at 5 min intervals.

Once the subject stopped using the handset for > 5 mins the target was set to zero, and the subject was observed until fully recovered. Once they were ready to walk they were tested for spontaneous and prompted recall of their keywords.

Statistical analysis

Volunteer characteristics and propofol concentration data are presented as median (range). Binary logistic regression was used to determine the effect-site propofol concentration and BIS value associated with 50% loss of memory for words. Logistic regression was used to analyse the correlation between BIS and blood and effect-site propofol concentrations.

RESULTS

Volunteer characteristics and main results are summarised in Table 18.1. When compared with the subjects in the study described in the chapter 17, the subjects were older (median (range): 38 (28 – 45) years vs. 32 (24 – 46) years, $P < 0.03$, Mann-Whitney U test), and there was a non-significant tendency for subjects in the current study to be heavier than in the previous study: 79 (63 – 110) kg vs. 69 (58 – 104) kg.

Somewhat higher blood and effect-site concentrations were reached in the current study. The median maximum (i.e. when the subjects stopped pressing the handset button) blood concentration was 2.4 (1.4 – 4.1) µg/ml, and the median maximum effect-site propofol concentration was 2.2 (1.2 – 3.9) µg/ml. At these concentrations, the OAA/S score was 4 in all but one volunteer, who, on reaching an effect-site concentration of 2.3 µg/ml had a score of 4 (responds to normal voice) for one minute, then a score of 3 (responds only to loud voice) for 3 min, and finally a score of 2 (responds to mild prodding/shaking). As a result the infusion was switched off, but

interestingly the OAA/S score remained <=3 until the estimated effect-site and blood propofol concentrations had decreased to 0.8 and 1.2 μg/ml respectively. There were no signs at any stage of respiratory depression.

The median (range) time to maximal sedation in this study was 33 (22 – 70) min. This was significantly faster than the time to maximal sedation in the previous study (median 65, range 30 – 110 min, $P < 0.001$, Mann-Whitney U test).

No volunteer had a decrease of more than 10% from baseline heart rate or blood pressure. Airway control was maintained in all subjects, but one volunteer had a brief self-limiting episode of oxygen desaturation to 88% (recovered to > 93% before supplemental oxygen could be administered). All other subjects had $SpO2 \geq 93\%$ throughout the study and did not require or receive supplementary oxygen.

BIS data were recorded automatically in 14 subjects – values up to the study endpoint are shown in Figure 18.3. Five volunteers had BIS values < 60 during the study. One, described above, had values between 50 and 60 when his OAA/S score was 2. The other 4 volunteers remained responsive to verbal command: 3 during episodes with the BIS 50 – 60, and 1 during several brief episodes when the BIS dropped into the 30's and 40's.

Correlation between BIS and effect-site propofol concentration

Figure 18.4 shows the relationship between BIS and effect-site propofol concentration. There was a weak linear correlation between the two variables ($P < 0.01$). The regression equation for this relationship is:

$$BIS = 95.8 - 8.68 \times \text{Effect-site propofol}$$

There was broad variability in the BIS values found at different effect-site propofol concentrations – this is reflected in the R^2 for the correlation, of 0.245. Some subjects

showed little change in the BIS until the effect-site propofol concentration had reached a threshold in the region of 1µg/ml, whereas other showed a progressive decline in BIS from very low propofol concentrations.

Correlation between effect-site propofol concentration and memory

There was a significant correlation between effect site propofol concentration (C_e) and likelihood of memory for words ($P < 0.001$, -2 log likelihood ratio 53.5). The C_e50 for loss of memory for words was 1.6 $\mu g.ml^{-1}$, based on the following logistic regression equation:

$$\text{Ln (Odds of loss memory for words)} = -2.375 + 1.483 \times C_e.$$

The odds for propofol having an effect on memory were 4.4 (95% CI: 1.6 – 12.0).

Correlation between BIS and memory

There was a significant correlation between BIS and loss of memory for words (-2 log likelihood 47.8). The binary logistic regression equation describing the relationship is:

$$\text{Ln (Odds of loss memory for words)} = 9.515 - 0.113 \times \text{BIS}$$

The BIS value associated with 50% loss of memory for words was 84.2.

DISCUSSION

To my knowledge this was the first ever use of effect-site targeted PMS. Effect-site targeting is intuitively attractive, because it enables small, almost step-wise changes in effect-site concentration. After a target increase a gradient between blood and effect-site concentration is generated for a brief period of time to increase the effect-site concentration, before the blood concentration is reduced to the new target concentration. By limiting the difference between the blood and brain concentrations, effect-site targeting may improve safety.

In this study, 16 volunteers using the system tried to stress the safety limits sufficiently to induce loss of consciousness, by repeatedly pressing the button of a patient control handset. At maximal sedation, 15 volunteers remained responsive to voice, whereas only 1 required greater stimulation (mild prodding). There were no episodes of apnoea or cardiovascular instability, but one volunteer had a brief self-limiting episode of oxygen desaturation. The volunteers achieved higher blood and effect-site propofol concentrations more rapidly than in the previous study using a blood-targeted TCI system, but with equivalent safety, and were ready to mobilise after a similar short recovery period.

There is a body of opinion in the United Kingdom, endorsed by the report of the Joint Working Party of the Royal College of Radiologists and Royal College of Anaesthetists, published in 1992, that loss of response to voice represents excessive sedation.[103] The guidelines published by the American Society of Anesthesiologists on their website are less rigorous, and define "moderate or conscious sedation" as a drug-induced state in which responsiveness to verbal and/or tactile stimulation is maintained, and in which cardiovascular function is "usually maintained" (http://www.asahq.org/publicationsAndServices/standards/20.htm). Given that our

study was performed within the United Kingdom it was our aim to develop a system that administered sedation according to the definition published by the Joint Working Party mentioned above. By this definition the volunteer who did not respond to voice was over-sedated, although most anaesthetists would agree that he was not unconscious. Most volunteers quickly became less sedated once the propofol infusion was switched off. Interestingly, many resumed pressing the control button within a few minutes of the infusion stopping (and believed that they had not stopped pressing the button!). The volunteer who lost responsiveness to voice remained in this state for a long time after the propofol infusion was stopped (until the blood and effect-site concentration had at least halved). This suggests that he might have lapsed into a sedative-assisted deep sleep. Indeed he was fatigued at the time, having been the junior doctor on call for the cardiac intensive care unit the night before. Had we recorded the unprocessed EEG during the study it might have been possible to later examine the trace and differentiate between natural sleep and drug-induced sedation (with the assistance of an expert neurophysiologist). It is unlikely that an increase in lockout period would have prevented this episode of oversedation.

With an effect-site targeted TCI system, the actual effect-site concentrations achieved depend on the rate of equilibration between blood and brain concentrations in the individual patient. [163] The k_{eo} used in the current study is the one used in the Diprifusor (0.27 min^{-1}), but a wide range of other values have been found or used in other studies (Billard: 0.2 min^{-1},[162] White: 0.20 min^{-1},[179] Schnider: 0.456 min^{-1},[163] Wakeling 0.63 min^{-1} [182]). These values correspond with $t_{1/2}$ k_{eo} (half-time of blood-brain equilibration) values between 1.1 and 3.5 min. The k_{eo} depends on the effect being measured, cardiac output and age (equilibration is slower, i.e. k_{eo} greater, in older patients).[183] Thus a k_{eo} value developed from population studies does not necessarily

apply to an individual. If the rate of equilibration in an individual is faster than the population value, then the effect-site concentrations achieved after an increase or decrease in target concentration will respectively temporarily overshoot or undershoot the target, with possible safety consequences. If, as in older patients, the rate of equilibration is slower than that found in the general population, then after an increase in target, the blood and effect-site concentrations will coincide below the target, before gradually increasing toward the target. This may of course be counteracted by the fact that other pharmacokinetic consequences of advanced age may cause the blood concentration to be higher than expected.

Although a linear correlation between effect-site propofol and BIS was found, there was wide variation in BIS values found at equivalent blood and effect-site propofol values (Figure 18.4). This is likely to be because of pharmacokinetic and pharmacodynamic differences between the volunteers, and possibly due to the limitations of the BIS algorithm particularly with regard to detection and rejection of EMG artefact in awake, talking subjects. Our findings were similar to those of other investigators who have studied propofol for sedation.[136;151] Leslie, in a study of the effects of propofol on learning and on the BIS, compared *measured* steady state propofol concentrations (after blood-brain equilibration) and found a similar variation, and a similar regression equation (BIS = 90 – 7.4 x [propofol]).[151] The correlation in Leslie's study was slightly better ($R^2 = 0.47$), possibly because she was using measured rather than estimated propofol concentrations.

There was a remarkable overlap in the range of concentrations at which memory was retained or lost. The lowest effect-site concentration at which memory was lost was 0.9 µg/ml (blood concentration 1.2 µg/ml). The highest concentration at which a word was remembered was 2.5 µg/ml (blood concentration 2.7 µg/ml). Six volunteers

remembered a total of 16 words presented to them when their effect-site concentrations were between 0.9 and 2.5 µg/ml (blood concentrations 1.2 and 2.7 µg/ml respectively). The C_e50 for loss of memory of words was somewhat higher than in the previous PMS study discussed in chapter 17 (1.6 versus 1.15 µg/ml), but there was a closer correlation in that study (-2 log likelihood 85.4 versus 53.5 in the current study). This value (of 1.6 µg/ml) is also much higher than that found in Leslie's study (0.66 µg/ml[151]). It is only possible to speculate about the reasons for these differences. As already mentioned, Leslie's study used a more rigorous model of learning. It also only involved males, whereas the current study involved males and females, and males are known to be more sensitive to the effects of propofol.[184]

During the conduct of the study, it became apparent that caution is required to protect the participants during such a study. One worrying feature was the degree of disinhibition shown by some volunteers, such that we made sure that there were always 2 investigators in the room with volunteers. Where possible, when the volunteer was female, we had another female in the room during the study. We made a point of not asking volunteers any questions other than about how they felt, to avoid precipitating answers or a train of thought that would otherwise have embarrassed the volunteer. Nonetheless, some spontaneously made some rather ribald comments, completely out of keeping with their usual character.

On a few occasions, 2 of the volunteers in this study made a motion with their hands that suggested that they mistakenly thought they had a glass in their hands and were trying to raise it to their lips. Self-sedation with propofol appeared to have an effect similar to mild alcohol intoxication, causing a relaxed warm pleasant euphoric feeling. Many volunteers made comments to this effect, as have several patients that I have sedated with propofol during my clinical practise. No difficulty was experienced in

recruiting volunteers for this study. Several had participated in previous propofol self-sedation studies, and many stated that they had enjoyed the experience.

A few interesting observations about memory during sedation were made. One volunteer recited passages of poetry (Milton and Homer) when moderately sedated. Later, she could not remember doing this, and more interestingly she also stated that she had not read these poems for many years, and was unaware that she could remember them! Unfortunately we did not think to check whether she was able to recite the same poems in a non-sedated state at a later date. An Italian volunteer, born in Eritrea, described in great detail the appearance of an Eritrean woman he had seen while on duty the night before. On questioning him later, he did not remember this discussion, and was amazed at the level of detail he had remembered. He had apparently only fleetingly noticed the woman when passing her in a corridor, and could not remember thinking about her features. These details appeared to have been processed unconsciously and to have been retrieved under the influence of propofol.

As mentioned in the results section several volunteers remained conscious, responding to verbal command, while registering BIS values in the 50s. One volunteer had several episodes lasting between 15 sec and 2 min during which his BIS fell sharply down to levels as low as 32 (Figure 18.3)! This casts further doubt on the wisdom of the manufacturers of the BIS monitor (Aspect Medical Systems) who recommend BIS values between 40 and 60 for surgical anaesthesia.

In conclusion, volunteers using an effect-site targeted TCI for self-sedation all reached an optimally sedated state, and did so more rapidly than in previous studies with a blood-targeted TCI system, but without loss of safety. No subjects lost consciousness, despite their best efforts. One subject became oversedated, but may have been asleep, and one other volunteer had a brief episode of oxygen desaturation below

90%. It is likely, but not certain, that these benefits will translate from the aritificial situation of non-stressed volunteers in a friendly atmosphere, to that of potentially unwell patients undergoing a stressful procedure. Further studies are required to test the system and concept in patients undergoing unpleasant and stressful procedures. In patients undergoing PMS who are not ASA physical status I routine oxygen administration is advisable. Finally, it is apparent that the BIS cannot be relied on exclusively to detect or prevent awareness. During surgical anaesthesia the anaesthetist should use the BIS in conjunction with the traditional signs of anaesthetic depth.

Table 18.1. Patient characteristics and main results

Age, years	37 (28-45)
Gender, n, male:female	11:5
Weight, kg	78 (63 –110)
Time to maximal sedation, min	33 (22 – 70)
Maximum effect-site propofol concentration ($\mu g.ml^{-1}$)	2.2 (1.2 – 3.9)
Minimum OAA/S score	2 (4 – 5)
Time between study end and mobilisation, min	17 (9 – 22)

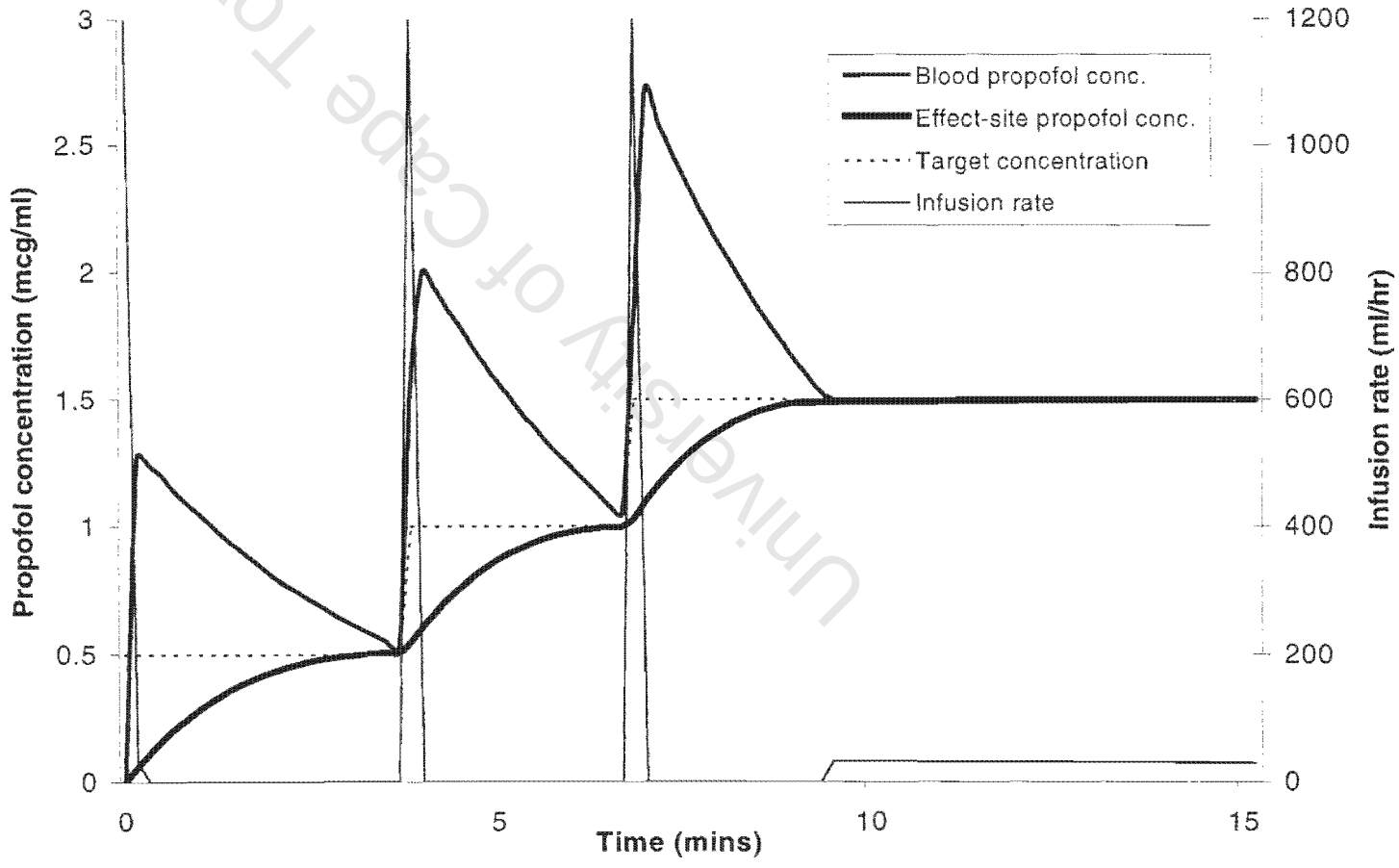


Figure 18.1: Effect-site targeted TCI. The figure illustrates 3 increases in target effect-site concentration. To generate the quickest possible increase in effect-site concentration, without an effect-site overshoot, the system calculates an optimal peak blood concentration. Once this concentration is reached the infusion is switched off. If the peak was correctly calculated the blood and effect-site concentrations will reach the target simultaneously. The system will then restart the infusion to maintain the blood and effect-site concentrations at the target concentration.

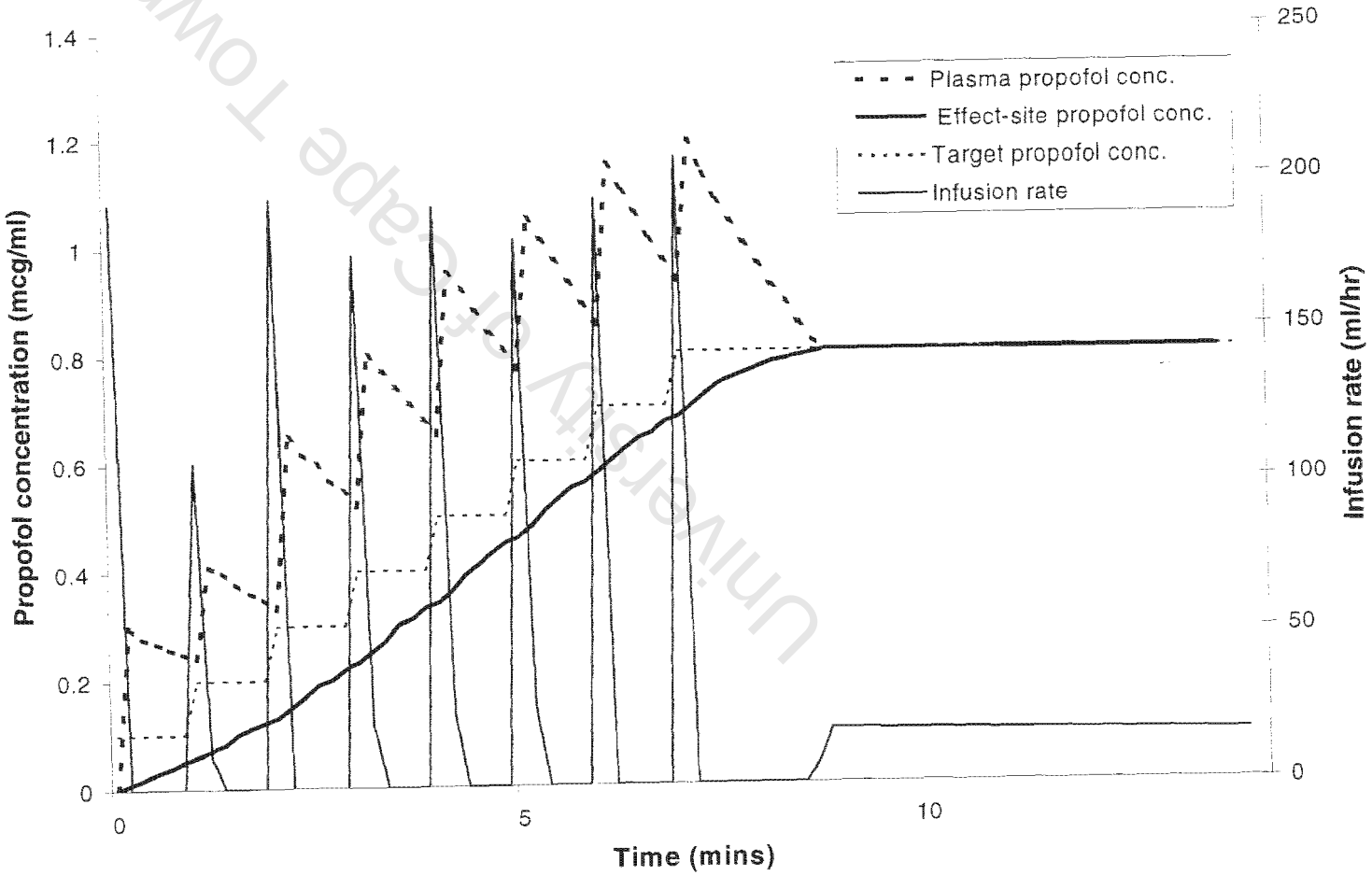


Figure 18.2: Effect-site targeted PMS. The graph shows the likely blood and effect-site propofol concentrations in a subject who continuously presses the button of an effect-site targeted PMS system with starting concentration 0, increment 0.1µg/ml, lockout 1 min

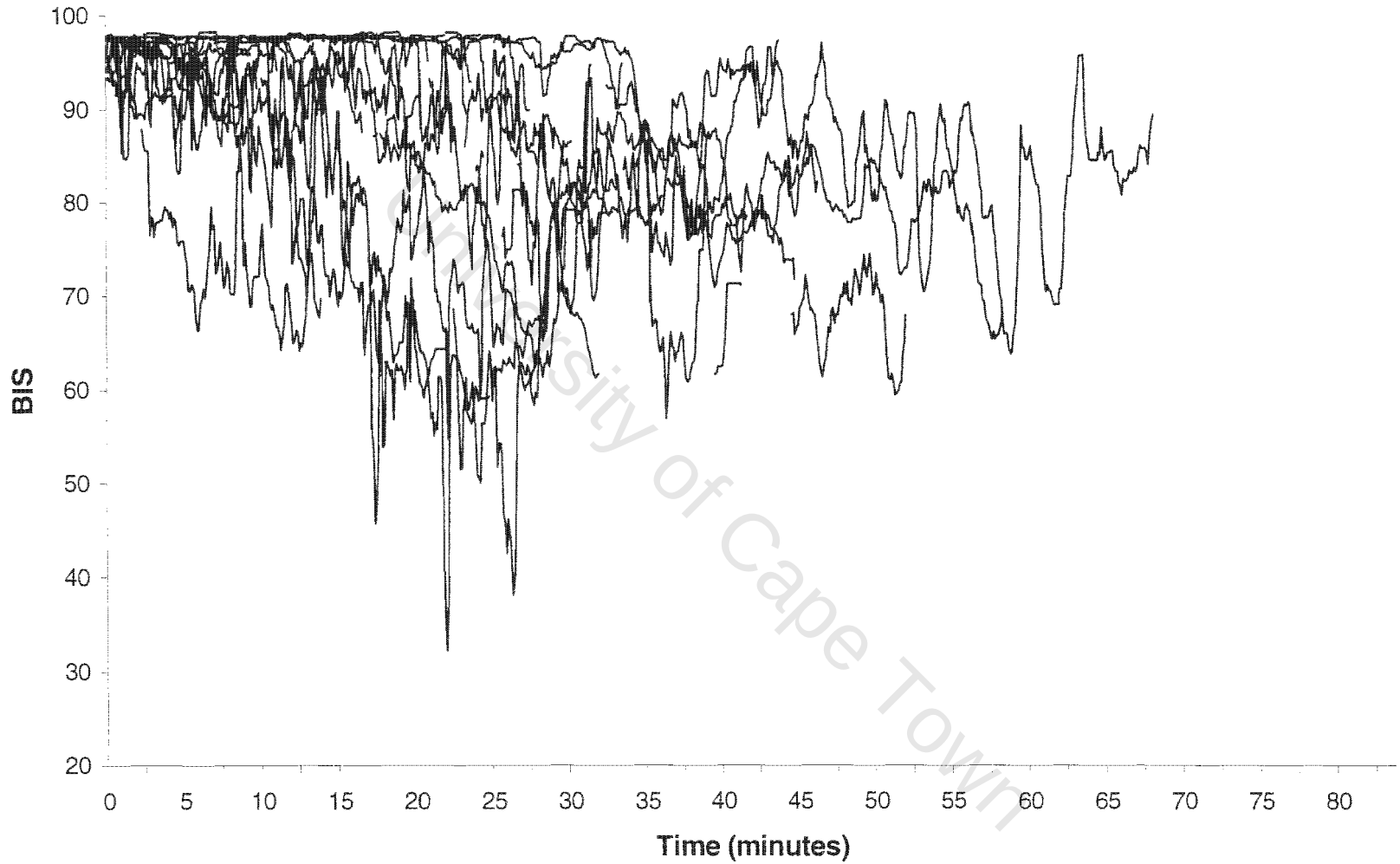


Figure 18.3: BIS data recorded automatically (every 5 sec) from 14 subjects. Each line represents the data from 1 subject. Note that the y-axis scale had been expanded to show greater detail in BIS values.

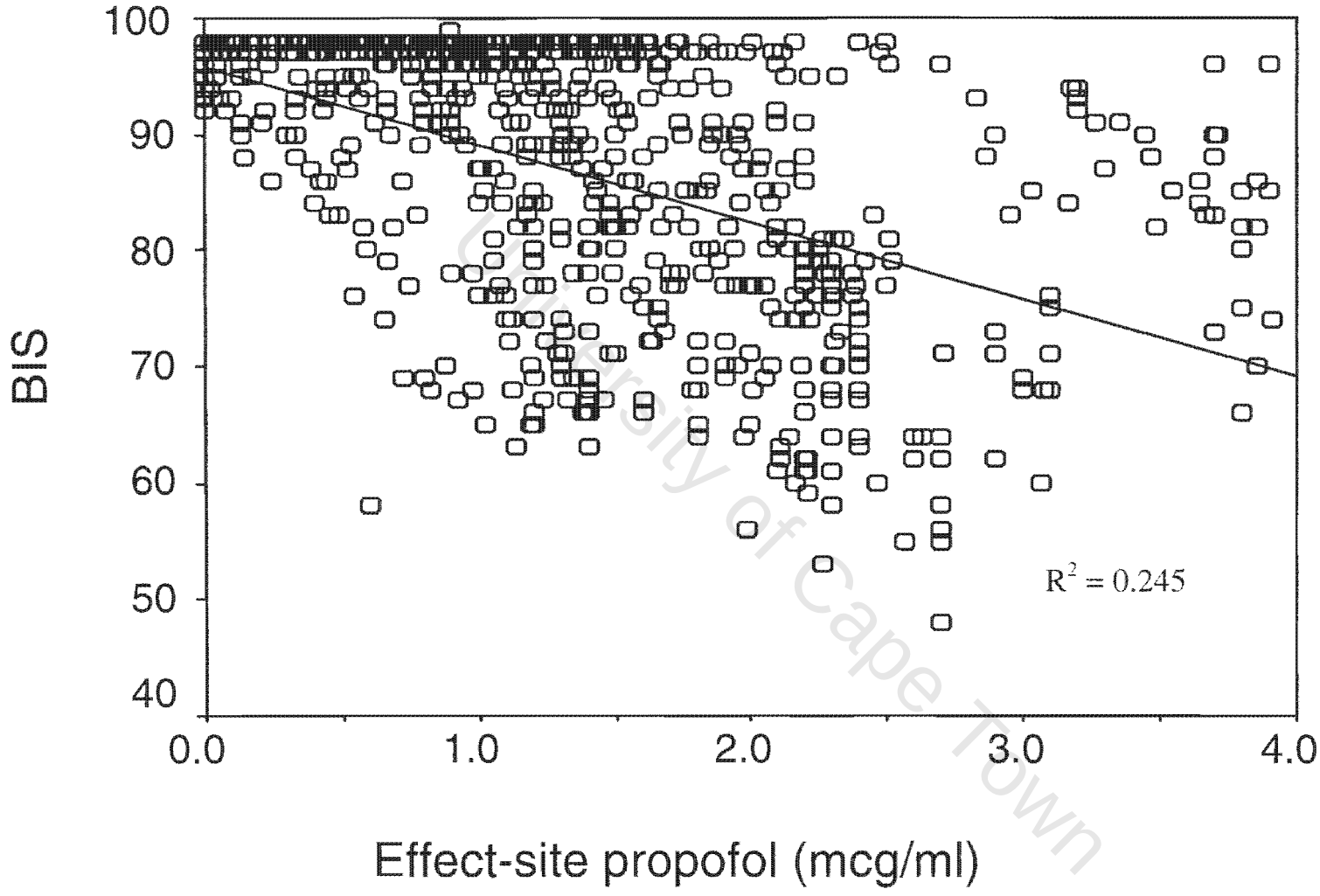


Figure 18.4: Scatter plot of BIS vs. effect-site propofol concentration with straight line indicating results of regression analysis

Chapter 19

Project 8: **Computer control of sedation using the BIS**

BACKGROUND

When physicians administer sedative agents for relief of anxiety or distress, one of the problems is the difficulty of judging the required dose. It is difficult to judge the degree of anxiety and distress experienced by another person; and there is a large degree of inter-individual pharmacokinetic variability and an even greater degree of pharmacodynamic variability. Two seemingly similar patients experiencing a similar degree of anxiety are unlikely to require and respond to the same dose. If an insufficient dose of drug is administered the patient will suffer discomfort leading to reduced satisfaction, and possibly impaired co-operation and sub-optimal operating conditions. An excessive drug dose will lead to oversedation and this may result in respiratory depression, loss of airway reflexes, and prolonged recovery.

In the previous two chapters the solution of feedback control by means of patient control of drug administration was explored. Another option is use an objective measure of stress or anxiety for feedback control. Unfortunately there is no such measure at present, but some of the newer variables derived from analysis of the surface EEG offer potential as surrogate measures. The BIS is a state-dependent measure of hypnosis: it decreases with natural sleep,[75] and with drug-induced sedation and hypnosis,[133;185] but these changes can be reversed by noxious stimuli. Thus when a sedative agent is administered during an unpleasant procedure, the BIS will give an indication of efficacy of treatment.

The favourable pharmacokinetic and pharmacodynamic profile of propofol makes it a suitable agent for sedation during unpleasant procedures such as

colonoscopy.[186] Thus closed loop administration of propofol using the BIS may improve the control of sedation. As described in chapter 9, BISCLAN uses a fixed control algorithm to calculate frequent small adjustments to the target propofol concentration based on frequent, objective assessments of the level of sedation or anaesthesia. These adjustments may result in more precise control than when the target propofol concentrations are controlled by a human in an open-loop manner.

The aim of the study was thus to investigate the effectiveness of BIS-guided feedback control of propofol administration for conscious sedation during colonoscopy.

METHODS

Closed loop system

The closed loop system has been described in detail in chapter 9. The control variable is the BIS, acquired in this study every 5 sec from an A-2000 BIS monitor using software version 3.4 (Aspect Medical Systems, Newton, USA). "BIS Sensor" electrodes (Aspect Medical Systems, Newton, USA), manufactured in a strip containing 3 "self-prepping" electrodes, were used to acquire the EEG signal. The control algorithm was the same as that used in the second half of the study described in chapter 14 – i.e. the same PID algorithm as shown in Appendix 1, but with effect-site steering (see Appendix 7). The control actuator is a TCI system controlled by a microprocessor programmed with the Marsh pharmacokinetic model.[43]

Study protocol

After Ethics Committee approval was sought and granted, 16 adult patients scheduled for elective day case colonoscopy were enrolled. To fulfil the entry criteria patients had

to provide written informed consent, be of ASA physical status I – III, and not have any known cerebral pathology or psychiatric disease that might alter the EEG waveform.

No sedative premedication was administered. A 22G cannula was inserted into a vein on the forearm or the dorsum of a hand, and 1ml (20 mg) of Buscopan (hyoscine butylbromide) was injected intravenously to relax the bowel. The BIS electrodes were attached and the impedances were checked. Once the impedances were all < 5000 Ω, BIS monitoring was commenced, with the BISCLAN program in "monitor" mode to automatically record the BIS every 5 sec. Routine physiological monitoring was instituted (heart rate, non-invasive arterial pressure, and oxygen saturation), and measurements were made and recorded every 5 min thereafter. The OAA/S rating scale (Table 5.1)[107] was used to assess sedation during induction and every 5 min thereafter. Recovery from sedation was assessed with a modified Aldrete score. [187]

Oxygen was administered at 4 l/min by facemask. The BISCLAN system was then switched to "manual" mode with a target propofol concentration of 2 µg/ml. The target concentration was increased by 0.5 µg/ml every minute until an OAA/S score of 3 (responds only if name called loudly or repeatedly) was reached. Once this goal was reached the BIS at that moment was noted, the system was switched to "maintenance" mode with that BIS as the set point, and the surgeon was invited to commence the procedure. If sedation became inappropriately light or deep during the procedure the BIS set point was altered by 5 units. Near the end of the procedure the system was switched back into manual mode, with the target propofol concentration set to zero.

The target propofol and the estimated blood and effect-site propofol concentrations were recorded automatically by the BISCLAN system. The following data were recorded manually: induction time (time to reach OAA/S 3), induction dose of propofol, total propofol dose, target propofol concentration, signs of inadequate

sedation such as movement or moaning, duration of closed loop control, and recovery time (time to an OAA/S score of 5 and an Aldrete score ≥ 8). During the recovery period the patients were asked about their experiences. Both the patient and the surgeon were asked to rate their satisfaction with the sedation on a 5 point score (where 1 represented very unsatisfied and 5 very satisfied).

Statistical analysis

Normally distributed data are presented as mean (standard deviation), and non-normally distributed data as median (range). To evaluate the control accuracy the following parameters were calculated for each patient: median BIS, median performance error (MDPE), median absolute performance error (MDAPE), wobble and divergence, as described in chapter 13 using the methods described and recommended by Varvel et al.[155] Offset (the difference between measured BIS and set point) and the proportion of BIS values within 5, 10 and 15% of the set point were also calculated. MDPE and offset are measures of bias, whereas the MDAPE is a measure of inaccuracy, and the proportions of BIS values within 5, 10 and 15% of set point are measures of precision or accuracy. Pearson correlation was used to examine the relationship between surgeon and patient satisfaction. Mann-Whitney U tests were used to compare non-parametric data. Statistical analyses were performed using Stata 6.0 software (Stata Corporation, Texas, USA). For differences to be considered statistically significant, $P < 0.05$ was required.

RESULTS

Nine woman and seven men, mean age 60 (16) years and mean weight 72 (11) kg were studied.

Mean induction time was 5 (2) min, and mean propofol induction dose 100 (32) mg. The median duration of closed loop sedation was 19 (7 – 50) min. During this time the median OAA/S score was 3 (2 – 4). Nine patients had OAA/S scores ≥ 3 during closed loop control. Seven patients had an OAA/S score of 2 for 25 (17 – 44)% of closed loop control time and an OAA/S score ≥ 3 for the remainder of the time. No patient became unrousable (OAA/S 1) during closed loop sedation. The blood propofol concentrations (as estimated by the Marsh model) during closed loop control are shown in Figure 19.1. For each patient the median target propofol concentration was calculated. The median (range) of these values during closed loop control was 2.3 (1.7 – 3.6) µg/ml. The maximum target propofol concentration at any time in any patient was 5.6 µg/ml (this patient required 160 mg of propofol to reach OAA/S 3) and the minimum target concentration at any time during closed loop control was 0.9 µg/ml (OAA/S score was 4 at the time).

Median BIS set point chosen at the end of induction was 80 (75 – 85). The set point was changed by 5 BIS units in 6 patients because of inadequate sedation. The performance characteristics of the system are summarised in Table 19.1. During closed loop control the median BIS was 79 (69 – 85), median MDPE was –1 (-9 – 6)% and median MDAPE was 7 (1 – 15), median wobble 6 (1 – 14)% and median divergence was 0 (-0.8 – 0.2) $BIS.hour^{-1}$. Offset values during closed loop control are shown in Figure 19.2. Mean offset was –1 (2) BIS units.

Respiratory and haemodynamic parameters were stable. Changes in these parameters are summarised in Table 19.2. No patients became apnoeic or required airway support while undergoing closed loop controlled sedation.

Half of the patients moaned or moved at some point during closed loop control. Median surgeon satisfaction score was 4 (2 – 5). Surgeon satisfaction score was

significantly better in those patients who did not move or moan ($P < 0.001$, Wilcoxon Rank Sum test). One patient recalled pain on injection of propofol and three patients remembered abdominal compression during closed loop control. The satisfaction scores were similar in patients with and without recall. One patient with recall had a satisfaction score of 2. Another patient (with no evidence of recall) had a satisfaction score of 3. The remaining 14 patients had a sedation satisfaction score of 5. There was no correlation between surgeon and patient satisfaction.

After the end of closed loop control it took a median of 4 (2 – 20) min for patients to reach an OAA/S score of 5 and a median time of 4 (1 – 18) min to reach an Aldrete score ≥ 8.

DISCUSSION

We set BISCLAN a very challenging control problem in this study. Despite this it performed remarkably well, with performance that was similar to that found in the two studies of BIS-guided control of general anaesthesia (chapters 13 and 14). There are no other published studies (on closed loop control of sedation) with which one can compare these results. Mortier and colleagues studied the use of a BIS-guided closed loop system (RUGLOOP) for sedation during surgery performed under regional anaesthesia. [160] Although RUGLOOP appeared to achieve stable BIS values, Mortier did not publish formal performance parameters. Moreover, in that study the BIS set point was low (64) and the patients were sedated to levels that, by some definitions, represent loss of consciousness (OAA/S = 1).[103] To our knowledge this current study was the first ever study of closed loop computer control of conscious sedation.

There are several reasons why sedation for colonoscopy is a challenging control problem. One is that patients undergoing colonoscopy experience **pain** in addition to

ignominy, anxiety, and distress. BISCLAN is only programmed to administer propofol, a drug that possesses sedative and anxiolytic properties, but is not an analgesic. Noxious stimuli can cause arousal, and reversal of sedation or general anaesthesia, thereby altering the pharmacodynamic relationship between dose and effect. In the two previous studies of BIS-guided closed loop control of anaesthesia (chapters 13 and 14) the control problem was somewhat simplified because pain was removed from the equation as analgesia was provided by either epidural analgesia or a TCI of remifentanil. Patients in the current study received an anti-muscarinic, but no analgesic. BISCLAN was thus required to control sedation in patients subjected to fluctuating levels of pain (caused by difficult passage of the endoscope, abdominal compression and bowel distension) using only a sedative agent.

Another reason why this was a challenging control problem is that the margin of error is much narrower during sedation than during general anaesthesia. Excessive sedation can lead to loss of airway reflexes, apnoea and aspiration, and has implications concerning the risk of bowel perforation (it has been suggested that if patients can respond to pain then colonic perforation may be more readily detected and prevented[188]). Noxious stimuli, on the other hand, can result in a rapid transition from adequate sedation to a fully awake, distressed and possibly uncooperative state. A third reason why this is a challenging control problem is that during sedation there is likely to be a large amount of artefact arising from movement and the resulting high-frequency EMG signals (from the ocular, facial and frontalis muscles).[189;190] When EMG artefact is recognised, the epochs containing it are excluded from the analysis, causing delays in updating of the BIS;[143] whereas when EMG artefact is not properly recognised it is likely to result in falsely elevated BIS levels. .[189]

There is an important balance to be achieved between optimising operating conditions and safety. Our goal was to produce "conscious sedation" – a drowsy state in which patients have relief of anxiety and amnesia, but remain responsive to command. When patients move, complain or moan, it is likely to distract the endoscopist, and may make the procedure technically more difficult to perform. It is natural that endoscopists may prefer their patients to be more deeply sedated or even unconscious, and indeed in this study the surgeon satisfaction score was higher when patients did not move or moan. Patients on the other hand were very satisfied with their sedation. All, but one, were completely satisfied and few had evidence of recall. Some patients were unresponsive to command for short periods during the study – but all responded to mild tactile stimulation – and none required airway support. Thus when propofol is administered by a closed loop system close observation by an anaesthetist is advisable.

The requirement for an anaesthetist to be present during closed loop sedation is unlikely to change, because stimulation alters the relationship between dose and effect. A computerised system cannot anticipate when noxious stimuli will occur or when they will stop, it can only react. Model-based closed loop systems may have an advantage over PID systems in this regard. For efficient operation, systems using PID algorithms depend on gain constants "tuned" for the general population. The equations and constants are fixed regardless of whether or not the patient is in pain. Model-based systems on the other hand can detect pharmacodynamic changes and make appropriate allowances. For example, during a painful stimulus the system will recognise that higher doses of propofol are required to achieve a given BIS, and the Hill Curve will be shifted to the right. Nonetheless no automated system can anticipate changes in the level of surgical stimuli. When a noxious stimulus is suddenly introduced or withdrawn, there will always be the risk of a change from adequate sedation to under- or oversedation

respectively. It is the latter that is most dangerous and requires the presence of an anaesthetist.

As in the previous studies with BISCLAN there was a degree of oscillation in several patients following a change in surgical stimulus. There are several possible solutions for this. Addition of an opioid analgesic is likely to dampen the response to painful stimuli (and would probably also have limited patient movement),[128] but is also likely to lead to more respiratory depression. Other solutions have been discussed previously, but include the use of an effect-site targeted TCI system, the use of a "self-tuning" PID algorithm, or a model-based algorithm. [191]

The aim of this study was to examine the effectiveness of BIS-guided closed loop propofol administration. It did not address the question of whether or not automatic control would provide improved safety or satisfaction when compared with anaesthetist or physician administered propofol (or other drugs for that matter). Most endoscopy procedures are performed under sedation administered by the operator. Mortality rates during endoscopy, particularly upper gastro-intestinal endoscopy, are very high when compared with those for general anaesthesia, [170] and future studies are needed to compare computer-administered sedation with operator-, anaesthetist- and patient-administered sedation.

In conclusion, BISCLAN was used to administer propofol sedation to a defined BIS value during colonoscopy, and succeeded in doing so safely and effectively. Surgeon and patient satisfaction were high, patients remained conscious at all times, and the measures of control performance were satisfactory.

Table 19.1. Performance characteristics of BIS-guided closed loop control

Performance indicator	Value
Set point	80 (75 – 85)
Median BIS	79 (69 – 85)
MDPE (%)	-1 (-9 – 6)
MDAPE (%)	7 (1 – 15)
Median wobble (%)	6 (1 – 14)
Divergence (BIS.hour $^{-1}$)	0 (-0.8 – 0.2)
Mean offset; BIS	-1 (2)
BIS values within 5% of set point (%)	36 (8 – 96)
BIS values within 10% of set point (%)	81 (28 – 100)
BIS values within 15% of set point (%)	96 (50 – 100)

Table 19.2. Summary of physiological parameters during closed loop control

Physiological parameter		
Heart rate (% change from baseline)	Maximum increase	0 (0 – 58)
	Maximum decrease	-13 (-50 – 0)
Systolic arterial pressure (% change)	Maximum increase	2 (0 – 40)
	Maximum decrease	-8 (-33 – 0)
Oxygen saturation (%)	Minimum overall	93

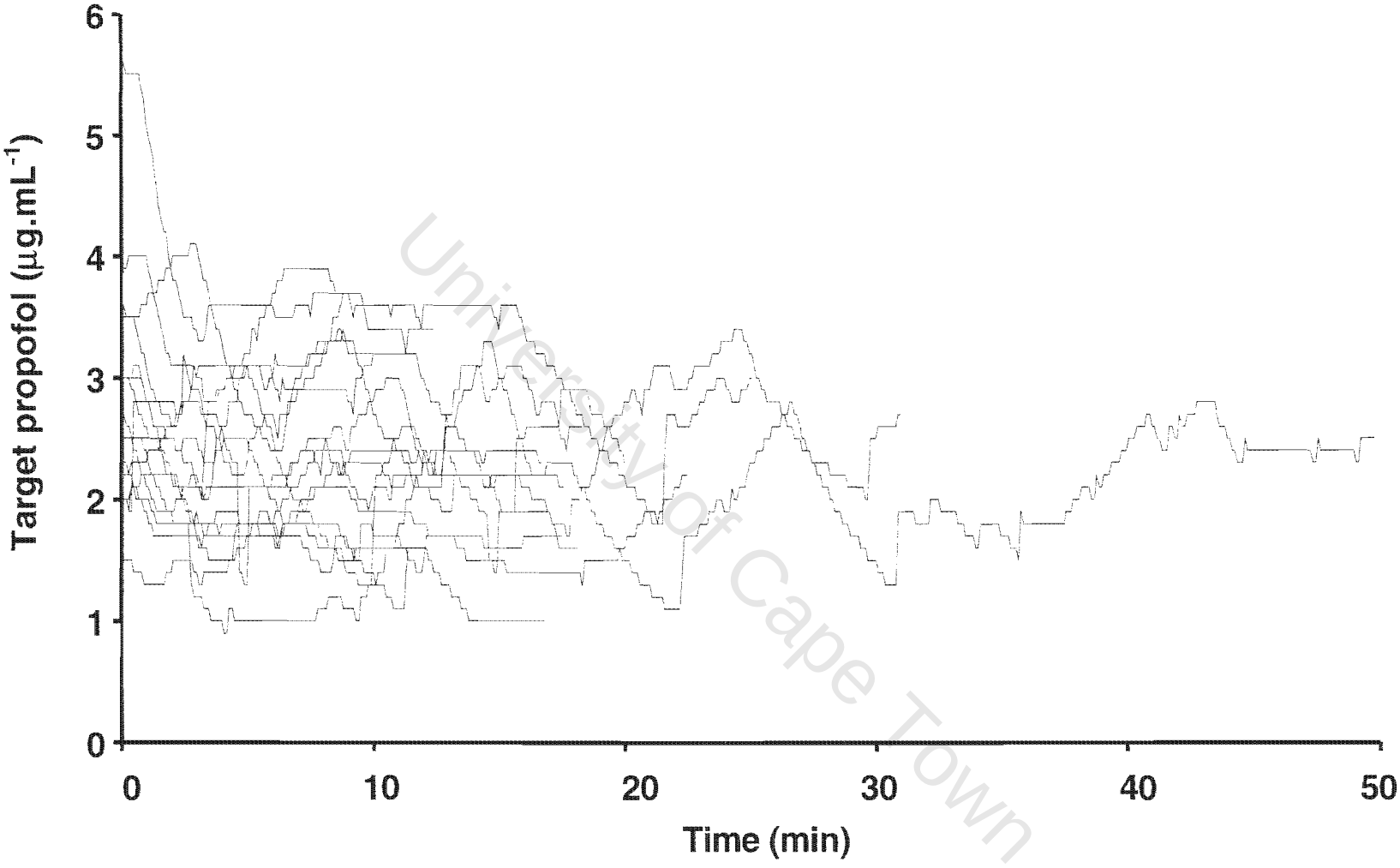


Figure 19.1: Blood propofol concentrations during closed loop control – each line represents data for one patient

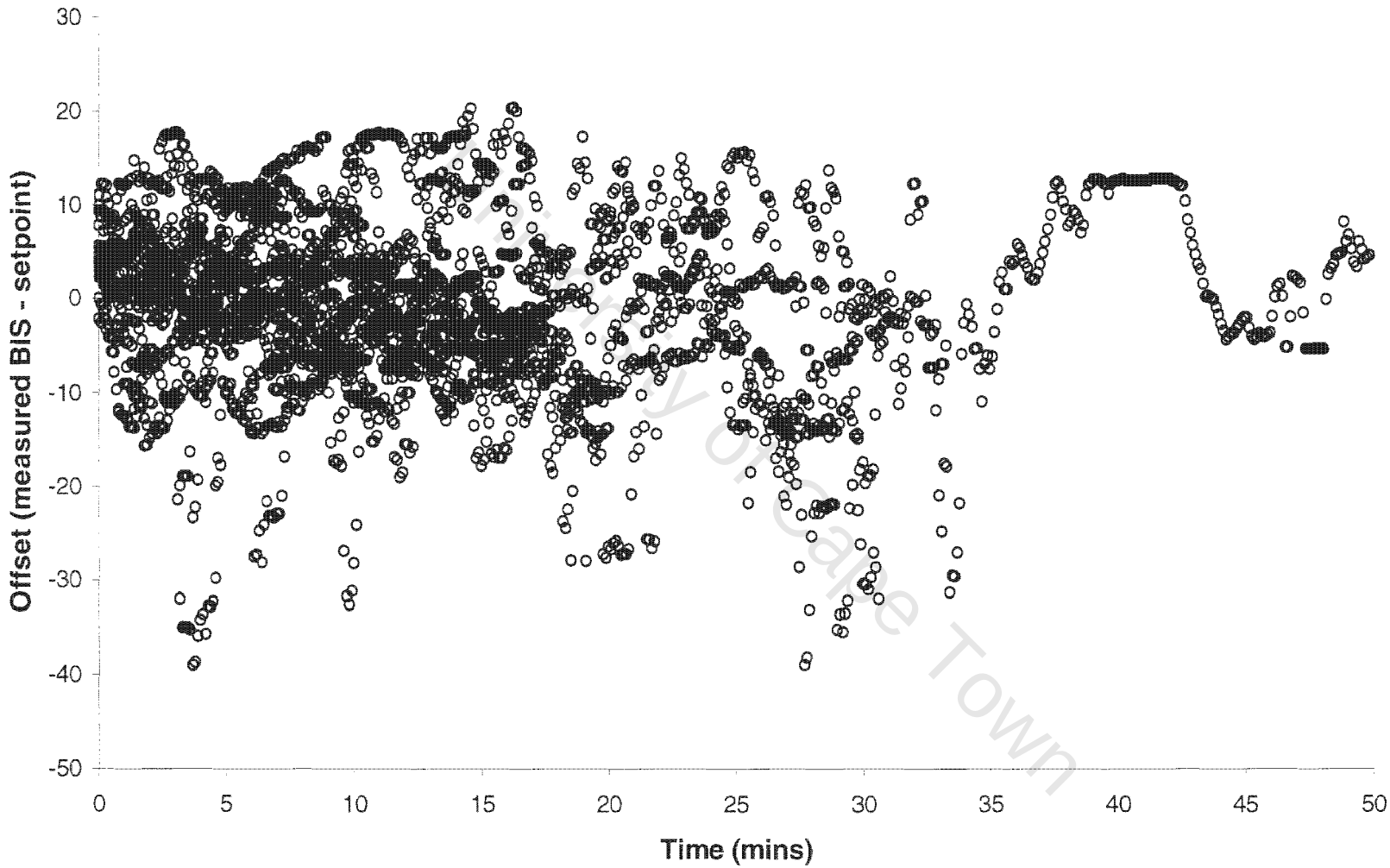


Figure 19.2: Offset values (measured BIS – set point) during closed loop control

Conclusion

Chapter 20

Conclusion

The discovery in the 1840s of a means of rendering patients unconscious during surgery was a major medical milestone. Although the early patients undergoing general anaesthesia were no doubt pleased to be unconscious during surgery, the early anaesthetic agents such as ether and chloroform had many serious adverse effects. Induction of, and recovery from anaesthesia was slow, unpleasant and dangerous.

Over the past century and a half many new drugs and techniques have been discovered and invented. "Cleaner" drugs, with better pharmacodynamic profiles, and fewer side effects, are now in daily use. Although anaesthesia is now very safe, with low morbidity and mortality rates, the introduction of balanced anaesthesia using intravenous hypnotics, neuromuscular blocking agents and manual control of ventilation, have introduced newer problems. One of these is the problem of inadvertent awareness during inadequate anaesthesia. Another is the problem of inadvertent loss of consciousness when sedation is intended (which can be more dangerous than planned general anaesthesia).

In the early days of anaesthesia, the fact that anaesthesia had to be induced and maintained via the inhalational route, and that these processes depended on the patients own respiratory drive, constituted a degree of feedback control of the administration of anaesthetic agents. When drugs are injected, patients are paralysed, or ventilation is controlled manually or by a machine, the anaesthetist has to control anaesthetic depth in an open loop manner. If he administers an inadequate dose of anaesthetic agent and the patient is paralysed then the patient is likely to regain consciousness during the operation with potentially devastating psychological consequences. To avoid this

problem, most anaesthetists err on the side of caution, and probably administer somewhat excessive doses of anaesthetic agents. Recently, investigators have begun to quantify the consequences of excessively deep anaesthesia. Early work suggests that excessively deep anaesthesia is associated with an increased one-year mortality in patients > 45 years old.[192-194]

Until recently anaesthetists have had to rely on clinical signs to judge the depth of anaesthesia or sedation, but these signs lack sensitivity and specificity. Although the published incidence of explicit awareness is now lower than ever before, the latest large study of awareness still showed an incidence of the order of 0.2%, slightly fewer than 1:500.[51] There is thus a need for better, more objective methods of measuring and controlling anaesthetic depth. As discussed in chapters 4 and 10, EEG-based measures, such as the BIS and the AEP show great promise, and indeed BIS monitoring has recently been shown to reduce the incidence of awareness.[57;195]

Computerised feedback control systems have the potential to exert more precise control over chemical and physiological systems than a human controlling anaesthesia in an open loop manner, but require a control variable that accurately reflects the state of the system. The lack of sensitivity and specificity of clinical signs means that it is unlikely that they can be used to successfully control anaesthesia or sedation. The aim of my studies was to investigate the safety and efficacy of two different closed loop control systems. The control variable for the first system, a computerised system, is the BIS, for which an anaesthetist chooses the set point. The developers of the BIS have calibrated it according to anaesthetists' impressions of anaesthetic depth, and it correlates well with blood hypnotic concentrations.

Numerous studies now use the BIS as the 'gold standard' against which new measures of anaesthetic depth are compared. Despite this, the BIS is not perfect. It

probably more accurately reflects the effect-site hypnotic concentration than the intrinsic brain state, providing an intravenous equivalent of an end-tidal volatile anaesthetic agent monitor. A combination of an opioid analgesic, and a hypnotic (propofol) were used in several of my studies. Although the opioids are known to potentiate the anaesthetic effects of the hypnotic agents, this is not usually reflected by a reduction in the BIS. In the presence of an opioid the relationship between effect-site hypnotic concentration and BIS is usually maintained, so that consciousness will be lost at a lower hypnotic concentration, and a higher BIS value, than in the absence of an analgesic agent.[196;197]. Also the relationship between the BIS and the likelihood of movement in response to pain is altered, so that at any given BIS value (even at quite high values), patients given large opioid doses are unlikely to move.[128] It is possible that this alteration is because the BIS reflects cortical activity, whereas in addition to effects at a cortical level, the opioids also exert powerful effects at sub-cortical and spinal levels. Functional imaging studies comparing responses to stimuli and regional metabolic changes may cast more light on the mechanism and significance of these interactions.

Despite the imperfections of the BIS, my studies have shown that a classical PID control algorithm using the BIS is able to provide satisfactory control of anaesthesia. An issue that has not been addressed is whether this automated system provided better control than that provided in the usual manner by an anaesthetist, in terms of improved post-operative recovery, improved patient satisfaction and reduced morbidity. To demonstrate the benefits of this and other automated systems for patients, rigorous double-blind controlled studies are required.

The control variable for the other system, a patient-controlled sedation system, is the emotional status of the patient (level of distress or anxiety), and here the patient

unconsciously chooses the set point. Factors that influence the set point at any one moment include: the noxious stimulus at that moment, the individual patients pharmacodynamic and pharmacokinetic make-up, expectations, pain threshold and tolerance of the adverse effects of the agent in use.

Before starting my studies I first had to develop a computerised system (which I called BISCLAN), capable of managing EEG data, capable of controlling a propofol TCI system, and finally also able to automatically control the infusion system using the BIS data in a feedback loop. This difficult task was successfully accomplished (Chapter 9), and the system was used in the other 7 projects that underpin this thesis. Two of the projects were studies that examined the BIS in greater detail, as part of a process of verifying its suitability as a control variable, and also to attempt to clarify the range of BIS set points that might be appropriate for sedation or anaesthesia. Using BISCLAN, two studies of the feasibility, safety and accuracy of automatic control of anaesthesia, and one study of the safety and accuracy of automatic control of sedation, were performed. Finally two studies of the safety of patient-maintained sedation were performed (during which BISCLAN was used to automatically record BIS data).

From my studies I can conclude the following:

1. Automatic feedback control of anaesthesia using the BIS as control variable
    a. It is possible to control anaesthesia using BISCLAN.
    b. Computer control of anaesthesia with BISCLAN software is associated with good cardiovascular stability in all patients, and adequate operating conditions in most patients
    c. Use of the BISCLAN system to control anaesthesia is associated with oscillation of the BIS and target propofol concentrations in some patients. This is probably

because the control algorithm parameters are not tuned for individual patients, and because of inherent sources of phase delay caused by the processing delay during the calculation of the BIS and by the delay in equilibration between the blood and effect-site propofol concentrations.

d. Computer simulations suggest that an adaptive model-based control algorithm and an effect-site targeted propofol infusion is associated with better stability and accuracy of the control variable than the (PID) control algorithm used in BISCLAN, when controlling anaesthesia with a BIS-guided feedback system.

e. Rigorous double-blind studies are required to demonstrate the benefit this system for patients in terms of outcome.

2. BIS-guided closed loop control of sedation

a. It is possible to control sedation during colonoscopy using BISCLAN

b. Computer control of sedation guided by the BIS is associated with good cardiovascular stability

c. Computer control of sedation, during colonoscopy, guided by the BIS is associated with good operator and patient satisfaction

d. Computer control of sedation, during colonoscopy, using BISCLAN, is associated with a ~ 50% incidence of moaning or movement that interferes with the procedure. This is probably because painful stimuli associated with the procedure cause arousal and distress that cannot be overcome simply by propofol (a hypnotic agent with no analgesic effects).

e. Rigorous double-blind studies are required to demonstrate the benefit of this system for patients in terms of outcome.

3. Regarding the Bispectral Index

   a. There is very broad variation in the BIS values found at defined clinical events such as loss of eyelash reflex, or eye opening on awakening. This is probably because of the processing delay inherent in the BIS calculation algorithm, differences between patients, and the limitations of the BIS and clinical signs as measures of anaesthetic depth.

   b. Consciousness is not infrequent at BIS values < 60

   c. The repetitive clicks generated by an AEP system do not alter the BIS

   d. BIS values present after recovery of consciousness do not predict working memory function, even in patients who have not received benzodiazepines

   e. BIS is able to predict the probability of recall of words presented to sedated volunteers. In the subjects I studied the BIS value associated with 50% loss of memory for words was 84, and the threshold BIS below which no key words were later remembered was 75.

   f. During sedation there is a weak linear correlation between BIS and effect-site propofol concentrations. Broad inter-individual variability limits the R^2 for this correlation to 0.245.

4. Patient-maintained sedation (PMS) using propofol by TCI

   a. When using a blood concentration targeted TCI for PMS a lockout period of 4 min and an increment of 0.1 µg/ml are associated with a lower risk of loss of consciousness than a lockout of 2 min and an increment of 0.2 µg/ml.

   b. For a distressed patient, repeatedly using the activating handset of a blood concentration targeted PMS, the lockout period should be longer than the time

required for blood-brain equilibration (> 10 min), and the increment should be small (0.1 μg/ml), to prevent any possibility of the patient:

i. Rendering himself unconscious.

ii. Suffering respiratory depression

Unless the starting target concentration is set to a high level, in many patients these settings will result in a long delay before optimal sedation is reached.

c. In the volunteers studied an effect-site targeted PMS system enabled volunteers to reach maximal sedation more rapidly than a blood concentration targeted PMS system, without any volunteers losing consciousness.

d. Maximal use of an effect-site targeted PMS system (by volunteers who pressed the activating button continually) resulted in a volunteer experiencing an adverse respiratory event (short-lived, self-limiting oxygen desaturation).

e. Healthy volunteers (and thus patients) using a PMS system sometimes experience respiratory depression (causing oxygen desaturation) without losing consciousness.

f. All patients or volunteers undergoing PMS should have pulse oximetry monitoring, and should receive supplemental oxygen.

g. Further studies are required to determine the safety of patient-maintained sedation in patients

h. Studies are required to determine if effect-site targeting improves the safety of a PMS system in patients.

i. Further studies are needed to compare the safety of PMS with open-loop physician-administered sedation.

5. Other:

   a. In the subjects studied the effect-site propofol concentration associated with 50% loss of memory for words was of the order of 1.2 – 1.6 µg/ml.

   b. AEP clicks, although loud, do not influence depth of anaesthesia in sedated or unconscious patients

   c. Research is hard work, but great fun!

The future

I believe that feedback control of anaesthesia and sedation is likely to become routine in the next few decades. In the context of control of sedation, patient control is likely to be the most effective and safest method. For anaesthesia, the control variable may or may not be based on the EEG. Before feedback control of anaesthesia or sedation can become routine several advances are required. A better understanding of the mechanism of action anaesthetic agents and of the nature of anaesthesia itself is required. Better measures of anaesthetic depth are needed, as are studies comparing and investigating other control methods such as neuro-fuzzy control.

Functional imaging techniques such as fMRI (functional magnetic resonance imaging) and PET (positron emission tomography) coupled with cognitive and neurological testing may shed light on the process of anaesthesia. Regions where function is either lost or maintained can be identified, and this information correlated with improved knowledge of the sites of action, and receptor systems influenced by, anaesthetic agents. At present I am involved in a study attempting to correlate neuro-psychiatric changes with alterations in regional function associated with low dose ketamine. In the future I hope to do similar studies involving drugs such as propofol.

The BIS is not a perfect measure of anaesthetic depth – there is a variable processing delay, the variability found at standard clinical end points is broad, there are paradoxical changes with some drugs such as ketamine and nitrous oxide, the monitor is very susceptible to artefact and the separation between conscious and unconscious values is insufficient. When the BIS is kept within the recommended range of 40 – 60 during surgery, later recall of intra-operative events is very unlikely. Unfortunately, these values do not guarantee unconsciousness, and can be associated with movement in response to noxious stimuli.

The EEG is a complex signal, representing the integrated or summated activity in the area of cortex close to the EEG electrodes. When using the EEG to quantify anaesthesia, the underlying assumption is that there is a close correlation between parameters of electrical activity (such as frequency, power and phase) and neurological function. Further assumptions are needed to believe that neurological function correlates with anaesthetic depth, and that there are thresholds of neurological function that can indicate the presence or absence of consciousness. The validity of these assumptions may or may not be verified in the future.

Existing functional imaging techniques quantify regional changes in functional parameters such as oxygen consumption or glucose metabolism. At present functional imaging techniques require bulky equipment, and lengthy data acquisition times. Future developments are likely, and it is possible that much smaller, portable scanners will be developed, and will themselves be suitable for use as near-real-time monitors of neurological function, and this may give a more direct indication of the effects of the anaesthetic agents and of anaesthetic depth. If such technology becomes available, and our understanding of the correlation between regional metabolic changes and neurological function improves, it might be possible to measure function in the areas of the brain known to be associated with consciousness, pain perception, or memory.

It is difficult to think of a single measure in medical practise where there is a precise cut-off value separating normal from abnormal values. More commonly there is a continuum, with different values associated with a greater or lesser probability of the presence of a specific state. No measure of anaesthetic depth is ever likely to be found that has a range of values that are 100% specific and 100% sensitive for loss of consciousness. It is more realistic to hope for a measure that is closer to real-time, has improved artefact detection and repair capabilities, applies to all anaesthetic agents, is

able to differentiate between sleep and anaesthesia, and is able to detect subtle changes in neurological function. If such a measure can be discovered then it will be possible to "calibrate" the monitor at the start of an anaesthetic, according to the responses of the patient, and to identify with greater certainty values that indicate the presence or absence of awareness. If an improved, more robust measure if found, there is no reason why automatic control of anaesthesia, using that measure as the control variable, should not be associated with very precise control of anaesthesia, and should not be used to routinely control anaesthesia. This does not mean that anaesthetists will become redundant – anaesthetists do far more than decide the anaesthetic dose, and of course machines cannot yet predict or anticipate when the surgeon or other personnel will introduce or withdraw a noxious stimulus.

It is likely that in the future more and more procedures will be performed under regional or local anaesthesia, thereby avoiding the need for general anaesthesia and its associated risks. Advances in local anaesthetic agents and regional anaesthetic techniques, coupled with advances in surgical and radiological techniques are likely to lead to greater availability of minimally invasive therapeutic treatments for patients previously considered too old or frail to withstand general anaesthesia for more invasive surgical procedures. This trend is already well underway, obvious examples being coronary angioplasty, and injection of oesophageal varices. Although much safer than open, more invasive surgical procedures, newer techniques may still be distressing or uncomfortable, and may require patients to lie motionless for periods of time. An increased use of conscious sedation techniques is thus also likely. As discussed in chapter 16, sedation, particularly in the hands of non-anaesthetists, is associated with significant morbidity and mortality. Feedback systems, which customise the dose of

sedative agent according to the exact requirements of the patient, are likely to be used more frequently.

For safer sedation, I believe that patient-maintained sedation systems are the way forward, and after further testing and refinements should enjoy the popularity and scope of use of patient-controlled analgesia systems. Currently available PMS systems rely on population-derived pharmacokinetic models. Future systems may incorporate parallel feedback systems that "tune" the pharmacokinetic model, or the system settings, for the specific patient. For example if a PMS system also incorporates a real-time objective measure of the effect of the sedative agent, the system might recognise that the k_{e0} of an individual patient is much higher or lower than the value in the average patient. In this case the system could then compensate for this by altering the lockout period, or revising the pharmacokinetic model. Another logical refinement would be to develop a PMS system that communicates with physiological monitors. The system could then be programmed to reduce the target concentration if the respiratory rate or the oxygen saturation decreases. Thus I believe that in future sedation might be provided by PMS systems, allowing patients to control the level of sedation according to their expectations and the other factors mentioned earlier, but with added safety provided by real-time measures of neurological, respiratory and cardiovascular function.

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Peer-reviewed publications relevant to this thesis

1. Absalom A, Sutcliffe N, Kenny GNC. Effect of the clicks of an AEP system on levels of consciousness and the Bispectral Index. *British Journal of Anaesthesia* 2001; 87(5): 778 – 80

2. Absalom A, Sutcliffe N, Kenny GNC. Closed loop control of anesthesia using Bispectral Index: performance assessment in patients undergoing major orthopedic surgery under combined general and regional anesthesia. *Anesthesiology 2002;* 96: 67-73

3. Leslie K, Absalom A, Kenny GN. Closed loop control of sedation in patients undergoing lower GI endoscopy. *Anaesthesia* 2002; 57(7): 693-7

4. Absalom A, Kenny GNC. Closed loop control of propofol anaesthesia using Bispectral Index: performance assessment in patients receiving computer-controlled propofol and manually-controlled remifentanil infusions for minor surgery. *British Journal of Anaesthesia 2003;* 90:737-41

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6. Struys MRF, De Smet T, Greenwald S, Absalom AR, Mortier EP. Performance Evaluation of Two Published Closed-loop Control Systems Using Bispectral Index Monitoring: A Simulation Study. *Anesthesiology* 2004; 100(3):640-647

List of relevant presentations to learned societies

1. Oral presentation: Closed loop control of anaesthesia. *West of Scotland and Glasgow Anaesthetic Research Club*, 1999
2. Oral presentation: Closed loop control of anaesthesia. *European Society for Technology in Anaesthesia and Intensive Care*, Glasgow 1999
3. Oral presentation: Closed loop control of anaesthesia using the Bispectral Index. *European Society for Intravenous Anaesthesia*, Amsterdam 1999
4. Poster presentation:Absalom AR, Sutcliffe N. Effect-site targeted patient-maintained sedation with propofol. *American Society of Anesthesiologists*, San Francisco 2000

   (Published abstract: Absalom AR, Sutcliffe N. Effect-site targeted patient-maintained sedation with propofol. *Anesthesiology* 2000; 93(Supplement): A291)
5. Poster presentation: Absalom AR, Kenny GNC. Closed-loop control of anaesthesia using the Bispectral Index. *American Society of Anesthesiologists*, San Francisco 2000

   (Published abstract: Absalom AR, Kenny GNC. Closed-loop control of anaesthesia using the Bispectral Index. *Anesthesiology* 2000; 93(Supplement): A292)
6. Oral presentation: Effect site targeted patient-maintained sedation with propofol. *Glasgow Anaesthetic Research Club*, 2000
7. Oral presentation: Effect-site targeted patient-maintained sedation. *EuroSIVA*, Vienna, 2000.
8. Poster presentation: Absalom AR, Sutcliffe N, Kenny GNC. Effect of the clicks of an AEP system on levels of consciousness and the Bispectral Index. *European Society of Anaesthesiology*, Gothenburg 2001

   (Published abstract: Absalom AR, Sutcliffe N, Kenny GNC. Effect of the clicks of an AEP system on levels of consciousness and the Bispectral Index. *Eur J Anaesth* 2001; 18 (Supplement 21): A-68)
9. Oral presentation: Clinical endpoints and Bispectral Index during Total Intravenous Anaesthesia. *European Society for Intravenous Anaesthesia*, Nice 2002

Appendix 1: list of files comprising BISCLAN, source code of main project file

When a program is developed using the Delphi rapid application development environment, 5 main types of file are generated. These file types are listed below, along with the names of the files that were developed for the BISCLAN project.

1. Project file – determines the order of appearance of the forms
   BISCLAN.dpr

2. Source files – contain the program source code
   EEGMonitorControl.pas – reproduced in Appendix 2
   BISCLANMainUnit.pas – reproduced in Appendix 3
   ControlAlg.pas – reproduced in Appendix 4
   StartUnit.pas – reproduced in Appendix 5
   TonyExtras.pas – reproduced in Appendix 6

3. Resource files – store the properties and objects for each form
   BISCLANMainForm.dfm
   StartForm.dfm
   EEGMonitor.dfm

4. Compiled unit files
   BISCLANMainUnit.dcu
   ControlAlg.dcu
   EEGMonitorControl.dcu
   StartUnit.dcu
   TonyExtras.dcu

5. Executable program file
   BISCLAN.exe

Source code for the main project file ("BISCLAN.dpr"):

```
program BISCLAN;

uses
  Forms,
  BISCLANMainUnit in 'BISCLANMainUnit.pas' {BISCLANMainForm},
  ControlAlg in 'ControlAlg.pas',
  EEGMonitorControl in 'EEGMonitorControl.pas' {EEGMonitorContrForm},
  StartUnit in 'StartUnit.pas' {StartForm},
  TonyExtras in 'TonyExtras.pas';

{$R *.RES}

begin
  Application.Initialize;
  Application.CreateForm(TStartForm, StartForm);
  Application.CreateForm(TBISCLANMainForm, BISCLANMainForm);
  Application.CreateForm(TEEGMonitorContrForm, EEGMonitorContrForm);
  Application.Run;
end.
```

Appendix 2: Source code for control algorithm:

```
unit ControlAlg;

interface

uses
  Windows, Messages, SysUtils, ExtCtrls, Series, ComCtrls, WinProcs,
  WinTypes, Classes, Graphics, Controls, Forms, Dialogs;

Type
  TrgtBloodPropArray = array[1..3] of Single;
  TControlAlg = class(TObject)
    private
    FAsaStatus: Integer;
    FTrgtPropValid: Boolean;
    FAutoMode: Integer;
    FMaxTrgtProp: Integer;
    FMinTrgtProp: Single;
    FContParmTrgt: Integer;
    FContParmVar: Integer;
    Procedure InitializeControlVars;
    Procedure SetMaxTrgtProp(MaxProp : Integer);
    Property AsaStatus: Integer Read FAsaStatus Write FAsaStatus;
    Property AutoMode: Integer Read FAutoMode Write FAutoMode;

  public
    Function CalcTrgtPropofol(ContParmActual:Integer; CalcBloodProp,
      EffProp:single):single;
    Function AdjustBloodPropTrgt(CalcBloodProp, EffProp: single):
      single;
    Procedure SetMinTrgtProp(MinProp : Single);
    Procedure SetVariance(Variance : Integer);
    procedure SetContParmTrgt(Target: Integer);
    constructor Create(aowner: TObject; ASA: Integer);
    destructor Free;

published
    Property MaxTrgtProp: Integer Read FMaxTrgtProp Write
    SetMaxTrgtProp;
    Property MinTrgtProp: Single Read FMinTrgtProp Write
      SetMinTrgtProp;
    Property ContParmVar: Integer Read FContParmVar Write SetVariance;
    property ContParmTrgt: Integer Read FContParmTrgt Write
       SetContParmTrgt;
  end;

const
  SecsPerDay = 60*60*24;
  ChangeInterval: array[1..3] of real = (10, 20, 40);      {seconds}
// Induction constants
  InitialTrgtBloodProp: array[1..3] of real = (4, 2, 1);
  StepTrgtBloodProp: array[1..3] of real = (1.5, 1.0, 0.5);
  wait: array[1..3] of integer = (40, 50, 60);
  waitFinal: array[1..3] of integer = (60, 60, 60);
  cutback: array[1..3] of real = (0.8, 0.8, 0.8);
// Maintenance constants
  MntTrgtPropEmerg: array[1..3] of real = (0.75, 0.5, 0.25);
  DeltaTrgtPropMax: array[1..3] of real = (3.0, 2.0, 1.0);
```

```
  MNTminProp = 1.0;
  Kp: array[1..3] of real = (0.3, 0.25, 0.2);
  Ki: array[1..3] of real = (0.075, 0.05, 0.025);
  Mntcutback: array[1..3] of real = (3.0, 2.0, 1.0);


var

 NewBIS, Error, ErrorOld, IndStepNo: Integer;
 TrgtBloodProp, CalcBloodProp, EffProp,
SumDeltaTrgtProp,DeltaTrgtProp:
      Single;
 IndFirstLoop, MntFirstLoop, TrgtPropChanged, IndEndFirstTime:
Boolean;
 IndTimer, MntTimeBase, MntTimer, IndTimeBase, TimeSinceLastChange,
      TimeOfLastChange: TDateTime;
 CurrentTime, TimePrevBIS, TimeCurrBIS: TDateTime;

Procedure Register;


implementation

{ Registration procedures }

procedure Register;
begin
  RegisterComponents('CLAN', [TComponent]);
end;


constructor TControlAlg.Create(aOwner: TObject; ASA: Integer);
  begin
    inherited Create;
    FAsaStatus := ASA;
    FAutoMode := AutoMode;
    InitializeControlVars;
  end;

destructor TControlAlg.Free;
  begin
    inherited Free;
  end;

Procedure TControlAlg.InitializeControlVars;
  Begin
    Case AutoMode of
// Induction mode
      2:
        begin
          IndFirstLoop := True;
          IndTimeBase := 0;
          IndTimer := 0;
          TrgtPropChanged := False;
          IndStepNo := 1;
          IndEndFirstTime := true;
          DeltaTrgtProp := 0;
        end;
// Maintenance mode
      3:
        begin
```

```
        end;
    end;
    FMaxTrgtProp := 15;
    FMinTrgtProp := 1;
    FContParmVar := 5;
    FAutoMode := 3;
    FContParmTrgt := 50;
    MntFirstLoop := True;
    MntTimeBase := 0;
    MntTimer := 0;
    TimeSinceLastChange := Time;
    TimeOfLastChange := Time;
    SumDeltaTrgtProp := 0;
    Error := 0;
    Errorold := 0;
    TrgtPropChanged := False;
  end;

Procedure TControlAlg.SetContParmTrgt(Target: Integer);
  begin
    if FContParmTrgt <> Target then FContParmTrgt := Target;
  end;

Procedure TControlAlg.SetMaxTrgtProp(MaxProp: Integer);
  begin
    if FMaxTrgtProp <> MaxProp then FMaxTrgtProp := MaxProp;
  end;

Procedure TControlAlg.SetMinTrgtProp(MinProp: Single);
  begin
    if FMinTrgtProp <> MinProp then FMinTrgtProp := MinProp;
  end;

Procedure TControlAlg.SetVariance(Variance: Integer);
  begin
    if FContParmVar <> Variance then FContParmVar := Variance;
  end;

// the main function - the control algorithm
Function TControlAlg.CalcTrgtPropofol(ContParmActual: Integer;
      CalcBloodProp, EffProp:single):single;
  begin
    TimePrevBIS := TimeCurrBIS;
    TimeCurrBIS := Time;
    if MntFirstloop = True then
      begin
        TrgtBloodProp := CalcBloodProp;
        MntFirstLoop := False;
        MntTimeBase := Time;
        MntTimer := 1/SecsPerDay;
        TimePrevBIS := Time;
      end;
    TimeSinceLastChange := Time - TimeOfLastChange;
    Error := ContParmActual - ContParmTrgt;
    if Abs(Error) <= ContParmVar then DeltaTrgtProp := 0 else
      DeltaTrgtProp := 0.03 * (Kp[ASAStatus] * (Error - ErrorOld) +
            Kp[ASAStatus] * (Ki[ASAStatus] * ((TimeCurrBIS-
            TimePrevBIS) * SecsPerDay) * Error));
    if ((CalcBloodProp >= TrgtBloodProp-5) and
      (CalcBloodProp<=TrgtBloodProp+5) and (TrgtBloodProp>=30))
      or ((CalcBloodProp>=TrgtBloodProp-10) and
```

```
            (CalcBloodProp<=TrgtBloodProp+10) and (TrgtBloodProp<30)
      and (TrgtBloodProp>2.0))
      or ((CalcBloodProp>=TrgtBloodProp-20) and
            (CalcBloodProp<=TrgtBloodProp+20) and (TrgtBloodProp<=20))
      or (Abs(ContParmActual - ContParmTrgt) > ContParmVar)
      or (abs(DeltaTrgtProp)>MNTTrgtPropEmerg[ASAStatus]) then
      begin
        if DeltaTrgtProp > DeltaTrgtPropMax[ASAStatus] then
              DeltaTrgtProp := DeltaTrgtPropMax[ASAStatus];
        SumDeltaTrgtProp:=SumDeltaTrgtProp+DeltaTrgtProp;
        if (TimeSinceLastChange >=
            (ChangeInterval[ASAStatus]/SecsPerDay))
            then
          begin
            TimeOfLastChange := Time;
            TrgtBloodProp := AdjustBloodPropTrgt(CalcBloodProp,
                  EffProp);
            SumDeltaTrgtProp:=0;
          end;
      end;
    ErrorOld := Error;
    MNTtimer := Time - MNTtimebase;
    if (MNTtimer > (180/SecsPerDay)) then
      begin
        MNTtimebase := Time;
        MNTtimer := 0;
        TrgtBloodProp := TrgtBloodProp - MNTcutback[ASAStatus];
      end;
    if TrgtBloodProp < MinTrgtProp then
      begin
        TimeOfLastChange := Time;
        TrgtBloodProp := MinTrgtProp;
      end;
    if TrgtBloodProp > MaxTrgtProp then
      begin
        TimeOfLastChange := Time;
        TrgtBloodProp := MaxTrgtProp;
      end;
    CalcTrgtPropofol := (round(TrgtBloodProp*10))/10;
  end;
end.
```

Appendix 3: source code of main program unit

(Main program loop is in procedure TBISCLANMainForm.MainProgramLoop)

```
unit BISCLANMainUnit;

interface

uses
  Windows, Messages, SysUtils, Classes, Graphics, Controls, Forms,
  Dialogs, TeeProcs, TeEngine, Chart, Menus, ExtCtrls, Series,
  StdCtrls, Buttons, ComCtrls, Grids, TonyExtras, EEGMonitorControl,
  Serial3, ControlAlg;

type
  TDataPositionArray = array[1..8] of Integer;
  TRunMode = (MonitorOnly, Manual, Induction, Maintenance);
  TBISCLANMainForm = class(TForm)
    PopupMenu1: TPopupMenu;
    Event: TMenuItem;
    Startofinduction: TMenuItem;
    Lossofconsciousness: TMenuItem;
    Intubation: TMenuItem;
    Startofsurgery: TMenuItem;
    Endofsurgery: TMenuItem;
    Eyesopen: TMenuItem;
    Respondstovoice: TMenuItem;
    RemembersDOB: TMenuItem;
    Freetext: TMenuItem;
    IntervalTimer: TTimer;
    SaveToDiskTimer: TTimer;
    PageControl1: TPageControl;
    TabSheet1: TTabSheet;
    BISChart: TChart;
    sbtnScrollBISRight: TSpeedButton;
    sbtnScrollBISLeft: TSpeedButton;
    sbtnBottomAxisZoomOut: TSpeedButton;
    sbtnBottomAxisZoomIn: TSpeedButton;
    sbtnLeftAxisZoomOut: TSpeedButton;
    sbtnLeftAxisZoomIn: TSpeedButton;
    sbtnRightAxisZoomOut: TSpeedButton;
    sbtnRightAxisZoomIn: TSpeedButton;
    Series1: TLineSeries;
    pnlControlPanel: TPanel;
    bbtnClose: TBitBtn;
    bbtnStartLogging: TBitBtn;
    bbtnStopLogging: TBitBtn;
    bbtnNewCase: TBitBtn;
    EventMemo: TMemo;
    pnlBIS: TPanel;
    lblBIS: TLabel;
    sbarBIS: TStatusBar;
    pnlBSR: TPanel;
    lblBSR: TLabel;
    sbarBSR: TStatusBar;
    StatusBar1: TStatusBar;
    TabSheet3: TTabSheet;
    lblBISTrgt: TLabel;
    sbtnDecBISTrgt: TSpeedButton;
```

```
sbtnIncBISTrgt: TSpeedButton;
BISTrgtEdit: TEdit;
lblMinProp: TLabel;
sbtnDecMinProp: TSpeedButton;
MinPropEdit: TEdit;
sbtnIncMinProp: TSpeedButton;
lblManBldProp: TLabel;
sbtnDecManBldProp: TSpeedButton;
ManBldPropEdit: TEdit;
sbtnIncManBldProp: TSpeedButton;
rgMode: TRadioGroup;
rbMonitorOnly: TRadioButton;
rbManual: TRadioButton;
rbInduction: TRadioButton;
rbMaintenance: TRadioButton;
GroupBox2: TGroupBox;
lblGrasebyPort: TLabel;
lblEEGPort: TLabel;
GrasebyPortEdit: TEdit;
EEGPortEdit: TEdit;
TabSheet2: TTabSheet;
Button1: TButton;
GrasebySerialComm: TSerial;
StatusBar2: TStatusBar;
Movement: TMenuItem;
Series2: TLineSeries;
Series3: TLineSeries;
Series4: TLineSeries;
sbtnDecBISVar: TSpeedButton;
BISVarEdit: TEdit;
sbtnIncBISVar: TSpeedButton;
lblBISVar: TLabel;
Button2: TButton;
BitBtn1: TBitBtn;
procedure sbtnScrollBISLeftClick(Sender: TObject);
procedure sbtnScrollBISRightClick(Sender: TObject);
procedure bbtnCloseClick(Sender: TObject);
procedure SetUpScreen;
procedure FormShow(Sender: TObject);
procedure UpdateTimeDatesbar;
Procedure WriteVarstoDisk(var NewValues: String);
procedure ParseIncomingDataString(var IncomingString: String);
Procedure UpdateBISGraph(NextBISValue: Integer);
Function CalcTimeElapsed(BaseTime:TDateTime): TDateTime;
procedure sbtnBottomAxisZoomOutClick(Sender: TObject);
procedure sbtnBottomAxisZoomInClick(Sender: TObject);
procedure bbtnStartLoggingClick(Sender: TObject);
procedure sbtnRightAxisZoomOutClick(Sender: TObject);
procedure sbtnLeftAxisZoomOutClick(Sender: TObject);
procedure sbtnLeftAxisZoomInClick(Sender: TObject);
procedure sbtnRightAxisZoomInClick(Sender: TObject);
procedure FreetextClick(Sender: TObject);
procedure EventMemoDblClick(Sender: TObject);
procedure AddEvent(Sender: Tobject);
procedure bbtnStopLoggingClick(Sender: TObject);
procedure MainProgramLoop;
procedure bbtnNewCaseClick(Sender: TObject);
procedure IntervalTimerTimer(Sender: TObject);
procedure SaveToDiskTimerTimer(Sender: TObject);
procedure rbMaintenanceClick(Sender: TObject);
procedure Button1Click(Sender: TObject);
```

```
    procedure GrasebySerialCommMessage(Sender: TObject; RxMessage:
            String);
    procedure rbManualClick(Sender: TObject);
    procedure rbMonitorOnlyClick(Sender: TObject);
    procedure sbtnDecBISTrgtClick(Sender: TObject);
    procedure sbtnDecMinPropClick(Sender: TObject);
    procedure sbtnDecManBldPropClick(Sender: TObject);
    procedure sbtnDecBISVarClick(Sender: TObject);
    procedure BISTrgtEditDblClick(Sender: TObject);
    procedure BISVarEditDblClick(Sender: TObject);
    procedure MinPropEditDblClick(Sender: TObject);
    procedure ManBldPropEditDblClick(Sender: TObject);
    procedure rgModeClick(Sender: TObject);
    procedure rbInductionClick(Sender: TObject);


 private

 public
    { Public declarations }
  end;


const
  BISScrollArrowIncrement = 50;
  ControlPanelWidth = 129;
  Border = 2;

// arrays of the positions of the BIS data in the monitor output
  A1000DataPositionArray : TDataPositionArray = (172, 179, 181, 188,
      217, 224, 244, 251);
  A2000DataPositionArray : TDataPositionArray = (73, 80, 82, 89, 100,
      107, 118, 125);

// Header arrays for the monitor data output
   Header1a = '  |  |  |  |  |S_HDR3              |SYS2.10|         |
            |         |         |          |         |Ch. 1   |         |
   |         |         |         |         |         |         |';
   Header1b = 'Ch. 2   |         |         |         |         |         |
   |         |         |Ch. 12   |         |         |         |         |
   |         |         |';
   Header2a = 'Mode|Events|TrgtProp|CalcBldProp|EffProp|BIStrgt|TIME
   |DSC      |PIC      |Filters  |Alarm    |Lo-Limit|Hi-Limit|Silence
   |SR09     |SEF06    |BISBIT00|B34U01   |TOTPOW06|EMGLOW01|SQI07
   |IMPEDNCE|ARTF2     |';
   Header2b = 'SR09     |SEF06    |BISBIT00|B34U01|TOTPOW06|EMGLOW01
   |SQI07    |IMPEDNCE|ARTF2     |SR09     |SEF06    |BISBIT00|B34U01
   |TOTPOW06|EMGLOW01|SQI07     |IMPEDNCE|ARTF2     |';
   A1000Hdr =Event|Date/time|Update|SpSmooth|BiSMooth|LoFilter
   |NotFilter|HiFilter|SpecSrt|BisArt|AbsDelta|AbsTheta|AbsAlpha|
   AbsBeta|TotPower|PBI|PBII|RelDelta|RelTheta|RelAlpha|RelBeta|
   PBRatio|SR|SEF|MF|Asym|BIS1|BIS2|BIS3|EMGHi|EMGLo';

var
  OldRunMode, NewRunMode, RunMode: TRunMode;
  FirstMainLoop: boolean;

//Interface vars
  BISCLANMainForm: TBISCLANMainForm;
  BISDisplayHistory, Count, InStringLength, BISTrgt, BISVar: Integer;
  ASAStatus, BISRecordNo, RecordNo, StrNo,Offset : Integer;
```

```
  AspectDataValid, AspectConnectionOK: Boolean;
  BISValid, SRValid, ReadyToLog, FirstLoop, OKtoContinue: Boolean;
  BISMonitor, NextString, AspectCtrlStr, PatientEvent: String;
  DataPositionArray: TDataPositionArray;
  ControlAlgorithm: ControlAlg.TControlAlg;

//Variables related to the BIS monitor
  TimeAspectInstructionSent, CurrentTime, TimePrevBIS,
            TimeCurrBIS: TDateTime;
  BIS, SR, SEF, EMGLow, NewBIS : Integer;

// Variables related to the TCI system
  TrgtBloodProp, MinTrgtProp: Single;
  GrasebyReplied, GrasebyReplyValid: Boolean;
  TimeLastGrasebyInstruction: TDateTime;
  GrasebyInstring : String;

 procedure SetUpParsingPositionArray;
 function GetCalcBloodPropConc: boolean;
 Procedure SendGrasebyInstruction(const Instruction: String);
 procedure AwaitGrasebyReply;
 procedure ParseAndValidateGrasebyReply;
 procedure HideModeRadiogroup;
 procedure ShowModeRadiogroup;
 procedure InitialiseCLANVars;
 procedure SetUpControlScreen;
 Procedure SetControlsStatus;

implementation

uses StartUnit;

{$R *.DFM}


Procedure TBISCLANMainForm.WriteVarstoDisk(var NewValues: String);
  var
    InitialString, Mode: String;
  begin
    if BISDataFileOpen then
      begin
        case RunMode of
          MonitorOnly: Mode := 'Mon';
          Manual : Mode := 'Man';
          Maintenance: Mode := 'Maint';
        end;
        StatusBar1.Panels[4].Text := 'Writing to disk';
        if ((FirstLoop) and (MonitorType = 'A2000')) then
          Begin
            FirstLoop := False;
            Write(BISDataFile, Header1a);
            WriteLn(BISDataFile, Header1b);
            Write(BISDataFile, Header2a);
            WriteLn(BISDataFile, Header2b);
          end
          else if ((FirstLoop) and (MonitorType = 'A1000')) then
            begin
              FirstLoop := False;
              WriteLn(BISDataFile, A1000Hdr);
            end;
        InitialString := Mode+'|'+PatientEvent+'|'+
```

```
            FloatToStr(TrgtBloodProp)+'|'+FloatToStr(CalcBloodProp)+
            '|'+FloatToStr(EffProp)+'|'+IntToStr(BISTrgt)+'|';
        Write(BISDataFile, InitialString);
        if MonitorType = 'A1000' then
            Write(BISDataFile, TimeToStr(Time), '|', '    2/5s|');
        Write(BISDataFile, NewValues);
        ReadyToLog := False;
        PatientEvent := '';
        SaveToDiskTimer.enabled := True;
        StatusBar1.Panels[4].Text := 'Data saved';
      end;
  end;

Procedure TBISCLANMainForm.UpdateBISGraph(NextBISValue: Integer);
begin
  Inc(BISRecordNo);
  With BISChart do
    begin
      if BISValid then
        BISCLANMainForm.Series1.AddXY(BISRecordNo, NextBISValue,
            TimeToStr(Time), clTeeColor)
        else
          BISCLANMainForm.Series1.AddXY(BISRecordNo, NextBISValue,
            TimeToStr(Time), clRed);
      if ((RunMode = Maintenance) or (RunMode = Manual)) then
        begin
          BISCLANMainForm.Series2.AddXY(BISRecordNo, CalcBloodProp,
            TimeToStr(Time), clTeeColor);
          BISCLANMainForm.Series3.AddXY(BISRecordNo, EffProp,
            TimeToStr(Time), clTeeColor);
        end;
      if RunMode = Maintenance then
        BISCLANMainForm.Series4.AddXY(BISRecordNo, BISTrgt,
            TimeToStr(Time), clBlue);
      BottomAxis.Maximum := BISRecordNo + Offset;
      BottomAxis.Minimum := BISRecordNo - BISDisplayHistory;
    end;
end;

procedure TBISCLANMainForm.sbtnScrollBISLeftClick(Sender: TObject);
begin
    With BISChart.BottomAxis do
      Offset := Offset + 50;
end;

procedure TBISCLANMainForm.sbtnScrollBISRightClick(Sender: TObject);
begin
    Offset := Offset - 50;
end;

Function TBISCLANMainForm.CalcTimeElapsed(BaseTime:TDateTime):
TDateTime;
  begin
    CurrentTime := Time;
    CalcTimeElapsed := CurrentTime - BaseTime;
  end;

Procedure TBISCLANMainForm.UpdateTimeDatesbar;
begin
     with StatusBar1 do
          begin
```

```
            panels[0].Text := DateToStr(Date);
            panels[1].Text := TimeToStr(Time);
          end;
end;

Procedure TBISCLANMainForm.SetUpScreen;
 var
   Index, ScreenWidth, ScreenHeight : Integer;
begin
    ReadyToLog := False;
    ScreenWidth := Self.Width;
    ScreenHeight := Self.Height;
    pnlBIS.Visible := True;
    BISCHart.visible := True;
// set up chart dimensions
  with BISChart do
      begin
        Left := 10;
        Width := ScreenWidth - ControlPanelWidth - 40;
        Top := 5;
        Height := Round(ScreenHeight * 0.80) - 5;
        with sbtnScrollBISRight do
          begin
            sbtnScrollBISRight.Top := BISCHart.Height -
                  sbtnScrollBISRight.Height - BISCHart.BevelWidth -
                  BISCHart.BorderWidth;
            sbtnScrollBISRight.Left := Parent.Width - Width -
                  BISChart.BevelWidth - BISChart.BorderWidth;
          end;
        with sbtnBottomAxisZoomOut do
          begin
            Top := sbtnScrollBISRight.Top;
            Left := BISChart.width - (2*sbtnScrollBISRight.Width) - 2;
          end;
        with sbtnScrollBISLeft do
          begin
            Top := sbtnScrollBISRight.Top;
            Left := BISChart.BevelWidth + BISChart.BorderWidth + 1;
          end;
        with sbtnBottomAxisZoomIn do
          begin
            Top := sbtnScrollBISRight.Top;
            Left := sbtnScrollBISLeft.Left + sbtnScrollBISLeft.Width;
          end;
        with sbtnLeftAxisZoomOut do
          begin
            Left := sbtnScrollBISLeft.Left;
            Top := BISChart.BevelWidth + BISCHart.BorderWidth + 1;
          end;
        with sbtnLeftAxisZoomIn do
          begin
            Left := sbtnLeftAxisZoomOut.Left;
            Top := sbtnLeftAxisZoomOut.Top +
                  sbtnLeftAxisZoomOut.Height;
          end;
        with sbtnRightAxisZoomOut do
          begin
            Left := sbtnScrollBISRight.Left;
            Top := sbtnLeftAxisZoomOut.Top;
          end;
        with sbtnRightAxisZoomIn do
```

```
          begin
            Left := sbtnRightAxisZoomOut.Left;
            Top := sbtnLeftAxisZoomIn.Top;
          end;
      end;
// set up control panel
    with pnlControlPanel do
      begin
        Left:= BISChart.Left + BISChart.Width + 5;
        Width  := ControlPanelWidth;
        Top := BISChart.Top;
        Height := (BISChart.Height div 2);
        with bbtnStartLogging do
          begin
            Top := pnlControlPanel.BevelWidth + Border;
            Height := Round((pnlControlPanel.Height - (2.5*Border) -
                  (BevelWidth * 2))/4);
            Left := pnlControlPanel.BevelWidth + Border;
            Width := Parent.Width-(pnlControlPanel.BevelWidth*2)-
                  (2*Border);
          end;
        with bbtnStopLogging do
          begin
            Top := bbtnStartLogging.Height + bbtnStartLogging.Top +
                  Round(Border/2);
            Height := bbtnStartLogging.Height;
            Left := bbtnStartLogging.Left;
            Width := bbtnStartLogging.Width;
          end;
        with bbtnNewCase do
          begin
            Top := bbtnStopLogging.Height + bbtnStopLogging.Top +
                  Round(Border/2);
            Height := bbtnStartLogging.Height;
            Left := bbtnStartLogging.Left;
            Width := bbtnStartLogging.Width;
          end;
       with bbtnClose do
         begin
           Top := bbtnNewCase.Height+bbtnNewCase.Top+Round(Border/2);
           Height := bbtnStartLogging.Height;
           Left := bbtnStartLogging.Left;
           Width := bbtnStartLogging.Width;
         end;
    end;
// set up BIS panel
   with pnlBIS do
     begin
       Left :=  pnlControlPanel.Left;
       Width := pnlControlPanel.Width;
       Top := pnlControlPanel.Top + pnlCOntrolPanel.Height + Border;
       Height := (pnlControlPanel.Height div 2) - Border;
       with lblBIS do
         begin
          Height := Round((pnlBIS.Height -
(2*sbarBIS.BorderWidth))/3);
          Top := pnlBIS.Top + BorderWidth;
         end;
       with sbarBIS do
         begin
           Height := lblBIS.Height * 2;
```

```
            Width := pnlBIS.Width - (2 * pnlBIS.BevelWidth);
            Top := lblBIS.top + lblBIS.Height + BorderWidth;
          end;
      end;
// set up BSR panel
    with pnlBSR do
      begin
        Left :=  pnlControlPanel.Left;
        Width := pnlControlPanel.Width;
        Top := pnlBIS.Top + pnlBIS.Height + (2 * Border);
        Height := pnlBIS.Height;
      end;
    with lblBSR do
      Height := lblBIS.Height;
    with sbarBSR do
      begin
        Height := sbarBIS.Height;
        Width := sbarBIS.Width;
        Top := sbarBIS.Top;
      end;
// Set up status bar - bottom of main screen
    with StatusBar1 do
      begin
        Panels[0].width := Round((Width - BevelWidth) * 0.8/7);
        Panels[1].width := Round((Width - BevelWidth) * 0.8/7);
        Panels[2].Width := Round((Width - BevelWidth) * 1.2/7);
        Panels[3].Width := Round((Width - BevelWidth) * 1.2/7);
        For Index := 4 to 6 do
          Panels[Index].Width := (Width - BevelWidth) div 7;
      end;
// Set up statusbar on bottom of controls screen
    with StatusBar2 do
      begin
        For Index := 0 to 4 do
          Panels[Index].Width := (Width - BevelWidth) div 5;
      end;
 end;

procedure TBISCLANMainForm.bbtnCloseClick(Sender: TObject);
  begin
    OKtoContinue := False;
    IntervalTimer.Enabled := False;
    if AspectStatus <> Idle then EEGMonitor.StopUpdates;
    bbtnStartLogging.Enabled := False;
    if MessageDlg('Are you sure you want to exit?',mtConfirmation,
        [mbYes, mbNo], 0) = mrNo then
        begin
          if StartForm.cbWriteBISToDisk.Checked then
            bbtnStartLogging.Enabled := True;
          bbtnClose.Enabled := True;
          bbtnNewCase.Enabled := True;
          OKToContinue := True;
          IntervalTimer.Enabled := True;
        end
        else
          begin
            if bbtnStartLogging.Enabled = True then Sleep(500);
            if BISDataFileOpen then CloseFile(BISDataFile);
              if BISSerialComms.Active then
                begin
                    BISSerialComms.Active := False;
```

```
                    BISSerialComms.Free;
                  end;}
                BISCLANMainForm.Close;
                StartForm.Close;
          end;
  end;

procedure SetUpParsingPositionArray;
  var
    Index: Integer;
begin
  if BISMonitor = 'A1000' then
    For Index := 1 to 8 do
      DataPositionArray[Index] := A1000DataPositionArray[Index]
  else
    For Index := 1 to 8 do
      DataPositionArray[Index] := A2000DataPositionArray[Index];
end;

procedure TBISCLANMainForm.FormShow;
  begin
    OKtoContinue := True;
    AspectStatus := Idle;
    Count := 0;
    FirstLoop := True;
    Offset := 40;
    UpdateTimeDatesbar;
    SetUpScreen;
    With BISChart do
      begin
        BISDisplayHistory := 120;
        AllowZoom := True;
        BottomAxis.Maximum := BISRecordNo + 20;
        BottomAxis.Minimum := BISRecordNo - BISDisplayHistory;
      end;
    if StartForm.cbWriteBISToDisk.Checked = true then
      bbtnStartLogging.Enabled := True;
    IntervalTimer.enabled := True;
    SetUpParsingPositionArray;
    RunMode := MonitorOnly;
    StatusBar2.Panels[0].Text := 'Monitor only mode';
    HideModeRadioGroup;
  end;

Procedure TBISCLANMainForm.ParseIncomingDataString(var IncomingString:
String);
  var
    Index: Integer;
    SRString, SEFString, BISString, EMGLowString : String;
begin
  BISValid := False;
// Get burst suppression ratio characters
  for Index := DataPositionArray[1] to DataPositionArray[2] do
    SRString := SRString + IncomingString[Index];
// check that the string is convertible to an integer, then convert
  if  MathsStuff.VerifyInteger(SRString) then
    begin
      SR := Round(StrToFloat(SRString));
      sbarBSR.Panels[0].Text := IntToStr(SR);
      SRValid := True;
    end
```

```
      else sbarBSR.Panels[0].Text := 'Invalid SR';
// Get SEF characters
  for Index := DataPositionArray[3] to DataPositionArray[4] do
    SEFString := SEFString + IncomingString[Index];
  if  MathsStuff.VerifyInteger(SEFString) then
    begin
      SEF := Round(StrToFloat(SEFString));
      StatusBar1.Panels[6].Text := 'SEF: '+ IntToStr(SEF);
    end;
// Get BIS characters
  for Index := DataPositionArray[5] to DataPositionArray[6] do
    BISString := BISString + IncomingString[Index];
  if  MathsStuff.VerifyInteger(BISString) then
    begin
      BIS := Round(StrToFloat(BISString));
      sbarBIS.Panels[0].Text := IntToStr(BIS);
      BISValid := True;
    end
      else sbarBIS.Panels[0].Text := 'Invalid BIS';
// Get EMGLow characters
  for Index := DataPositionArray[7] to DataPositionArray[8] do
    EMGLowString := EMGLowString + IncomingString[Index];
  if  MathsStuff.VerifyInteger(EMGLowString) then
    begin
      EMGLow := Round(StrToFloat(EMGLowString));
      StatusBar1.Panels[5].Text := 'EMGLow: '+ IntToStr(EMGLow);
    end;
end;

procedure TBISCLANMainForm.sbtnBottomAxisZoomOutClick(Sender:
TObject);
begin
  BISDisplayHistory := Round(BISDisplayHistory*1.1);
end;

procedure TBISCLANMainForm.sbtnBottomAxisZoomInClick(Sender: TObject);
begin
  BISDisplayHistory := Round(BISDisplayHistory/1.1);
end;

procedure TBISCLANMainForm.sbtnRightAxisZoomOutClick(Sender: TObject);
begin
  with BISChart.RightAxis do
    Maximum := Maximum * 1.1;
end;

procedure TBISCLANMainForm.sbtnLeftAxisZoomOutClick(Sender: TObject);
begin
  with BISChart.LeftAxis do
    Maximum := Maximum * 1.1;
end;

procedure TBISCLANMainForm.sbtnLeftAxisZoomInClick(Sender: TObject);
begin
  with BISChart.LeftAxis do
    Maximum := Round(Maximum/1.1);
end;

procedure TBISCLANMainForm.sbtnRightAxisZoomInClick(Sender: TObject);
begin
  with BISChart.RightAxis do
```

```
    Maximum := Round(Maximum/1.1);
end;

procedure TBISCLANMainForm.FreetextClick(Sender: TObject);
begin
  EventMemo.Visible := True;
end;

procedure TBISCLANMainForm.EventMemoDblClick(Sender: TObject);
begin
  EventMemo.Visible := False;
  PatientEvent := EventMemo.Text;
  EventMemo.Lines.Clear;
end;


procedure TBISCLANMainForm.MainProgramLoop;
var
  NextDataString: String;
begin
  if OKtoContinue then
  begin
  IntervalTimer.enabled := False;
  Application.ProcessMessages;
  Inc(Count);
  NextDataString := EEGMonitor.GetNextDataString;
  UpdateTimeDatesbar;
  Application.ProcessMessages;
  if NextDataString = '' then
      StatusBar1.Panels[2].Text := 'Aspect Comms problem'
    else
    begin
      StatusBar1.Panels[2].Text := 'Aspect comms OK';
      StatusBar2.Panels[2].Text := 'Aspect data received';
        if (ReadyToLog) then
          begin
            SaveToDiskTimer.enabled := False;
            WriteVarstoDisk(NextDataString);
          end;
      ParseIncomingDataString(NextDataString);
      if ((RunMode = Induction) or (RunMode = Maintenance)) then
        begin
          if BISValid then
            if SR = 0 then
              TrgtBloodProp := ControlAlgorithm.CalcTrgtPropofol(BIS,
                  CalcBloodProp, EffProp)
                else if SR > 0 then TrgtBloodProp :=
                  TrgtBloodProp*0.98;
          if TrgtBloodProp < MinTrgtProp then TrgtBloodProp :=
                  MinTrgtProp;
        end;
    end;
  if ((RunMode = Manual) or (RunMode = Maintenance)) then
    begin
      SendGrasebyInstruction(FloatToStr(Round(TrgtBloodProp*10)));
      AwaitGrasebyReply;
      ParseAndValidateGrasebyReply;
      Application.ProcessMessages;
    end;
  UpdateBISGraph(BIS);
  IntervalTimer.Interval := 50;
```

```
  IntervalTimer.Enabled := True;
  end;
end;

procedure TBISCLANMainForm.bbtnStartLoggingClick(Sender: TObject);
  begin
    bbtnStartLogging.Enabled := False;
    bbtnStopLogging.Enabled := True;
    bbtnClose.Enabled := False;
    ReadyToLog := True;
  end;

procedure TBISCLANMainForm.AddEvent(Sender: TObject);
begin
  if PatientEvent <> '' then PatientEvent := PatientEvent + '|';
  If Sender = StartOfInduction then
      begin
        PatientEvent := PatientEvent + 'Induction';
      end;
  If Sender = LossOfConsciousness then
      begin
        PatientEvent := PatientEvent + 'LOC';
      end;
  If Sender = Intubation then
      begin
        PatientEvent := PatientEvent + 'Intubation';
      end;
  If Sender = StartOfSurgery then
      begin
        PatientEvent := PatientEvent + 'SurgeryStart';
      end;
  If Sender = Movement then
      begin
        PatientEvent := PatientEvent + 'Movement';
      end;
  If Sender = EndOfSurgery then
      begin
        PatientEvent := PatientEvent + 'SurgeryEnd';
      end;
  If Sender = EyesOpen then
      begin
        PatientEvent := PatientEvent + 'EyesOpen';
      end;
  If Sender = RespondsToVoice then
      begin
        PatientEvent := PatientEvent + 'Voice';
      end;
  If Sender = RemembersDOB then
      begin
        PatientEvent := PatientEvent + 'DOB';
      end;
end;

procedure TBISCLANMainForm.bbtnStopLoggingClick(Sender: TObject);
begin
  bbtnStartLogging.Enabled := False;
  bbtnStopLogging.Enabled := False;
  ReadyToLog := False;
  bbtnClose.enabled := False;
  Application.ProcessMessages;
  bbtnStartLogging.Enabled := True;
```

```
  bbtnClose.enabled := True;
  bbtnNewCase.enabled := True;
end;

procedure TBISCLANMainForm.bbtnNewCaseClick(Sender: TObject);
begin
  if MessageDlg('Are you sure you want to change to a new case?',
   mtConfirmation, [mbYes, mbNo], 0) = mrYes then
   begin
     ReadyToLog := False;
     IntervalTimer.enabled := False;
     SaveToDiskTimer.enabled := False;
     Sleep(1000);
     Application.ProcessMessages;
     if BISDataFileOpen = True then
       if StartForm.CloseCurrentFile then BISDataFileOpen := False;
     BISCLANMainForm.Close;
     StartForm.Show;
   end;
end;

procedure TBISCLANMainForm.IntervalTimerTimer(Sender: TObject);
begin
  if OKtoCOntinue then MainProgramLoop;
end;

procedure TBISCLANMainForm.SaveToDiskTimerTimer(Sender: TObject);
begin
  if OKtoContinue then ReadyToLog := True;
end;

procedure TBISCLANMainForm.rbMaintenanceClick(Sender: TObject);
begin
  if RunMode = Maintenance then HideModeRadioGroup else
    begin
      if MessageDlg('Are you sure you want to change to maintenance
            mode?',
        mtConfirmation, [mbYes, mbNo], 0) = mrYes then
          begin
            EEGMonitor.StopUpdates;
            if not GrasebySerialComm.Active then
                  GrasebySerialComm.Active := True;
            if GetCalcBloodPropConc then
              begin
                RunMode := Maintenance;
                if not Assigned(ControlAlgorithm) then
                  ControlAlgorithm := TControlAlg.Create(self,
                        ASAStatus);
                InitialiseCLANVars;
                SetUpControlScreen;
                IntervalTimer.Enabled := True;
                StatusBar2.panels[0].Text := 'Maintenance';
              end
             else ShowMessage('Sorry, there is a problem with the
                  Graseby connection. Closed loop control is not
                  currently   possible.');
          end
            else HideModeRadioGroup;
    end;
end;
```

```
Function GetCalcBloodPropConc: boolean;
  begin
    Result := False;
    SendGrasebyInstruction('');
    BISCLANMainForm.StatusBar2.panels[2].Text := 'Waiting for Graseby
      reply';
    Application.ProcessMessages;
    AwaitGrasebyReply;
    ParseAndValidateGrasebyReply;
    if GrasebyReplyValid then Result := True;
  end;

Procedure SendGrasebyInstruction(const Instruction: String);
begin
  GrasebyReplied := False;
  BISCLANMainForm.GrasebySerialComm.WriteString(': ' + Instruction +
      Char(13) + Char(10));
  Application.ProcessMessages;
  TimeLastGrasebyInstruction := Time;
  BISCLANMainForm.UpdateTimeDatesbar;
  BISCLANMainForm.StatusBar2.Panels[3].Text := 'Graseby instruction
      sent';
  BISCLANMainForm.StatusBar2.Panels[4].Text := 'Waiting for Graseby
      reply';
end;

procedure TBISCLANMainForm.Button1Click(Sender: TObject);
begin
  IntervalTimer.Enabled := False;
  ShowModeRadiogroup;
end;


Procedure AwaitGrasebyReply;
  var
    Count : Integer;
begin
  Count := 0;
  BaseTime := Time;
  GrasebyReplied := False;
  Repeat
    begin
      BISCLANMainForm.StatusBar2.Panels[4].Text := 'Waiting for
Graseby
            reply';
      Application.ProcessMessages;
      if TonyExtras.TimeCalc.CalcTimeElapsed(BaseTime) > 5/SecsPerDay
then
        begin
          BaseTime := Time;
          Count := Count + 1;
          BISCLANMainForm.StatusBar1.Panels[3].Text := 'Graseby reply
            is delayed';
        end;
      if Count = 2 then
        begin
          BISCLANMainForm.StatusBar1.Panels[3].Text := 'Graseby time
            out problem';
          Exit;
        end;
    end;
```

```
  Until Length(GrasebyInstring) > 1;
end;

procedure TBISCLANMainForm.GrasebySerialCommMessage(Sender: TObject;
  RxMessage: String);
begin
  GrasebyInstring := RxMessage;
  GrasebyReplied := True;
  StatusBar1.Panels[3].Text := 'Graseby Comms OK';
  StatusBar2.Panels[4].Text := 'Graseby Reply received';
end;

procedure ParseAndValidateGrasebyReply;
  var
    StringLength, HashPos: Integer;
    EffPropString, BloodPropString: String;
  begin
      StringLength := Length(GrasebyInstring);
      HashPos := Pos('#', GrasebyInstring);
// Check that string has valid structure
      if Length(GrasebyInstring) > 0 then
        begin
          if ((GrasebyInstring[1] = ':') and
            (GrasebyInstring[StringLength] = #$D))
            then GrasebyReplyValid := True
            else
              begin
                GrasebyReplyValid := False;
                exit;
              end;
        end
        else
          begin
            BISCLANMainForm.StatusBar2.panels[2].Text := 'Graseby
comms
                  problem';
            BISCLANMainForm.StatusBar2.panels[2].Text := 'No Graseby
                  reply';
            BISCLANMainForm.StatusBar2.color := clRed;
            exit;
          end;
// Extract calculated blood propofol concentration
      BloodPropString := Copy(GrasebyInstring, 2, (HashPos - 2));
// Check that BloodProp characters are a number before converting
      if TonyExtras.MathsStuff.VerifyInteger(BloodPropString) then
        CalcBloodProp := StrToInt(BloodPropString)/10;
// Extract calculated effect site propofol concentration
      EffPropString := Copy(GrasebyInstring, (HashPos + 1),
(StringLength - HashPos - 1));
// Check that Effect Prop characters are a number before converting
      if TonyExtras.MathsStuff.VerifyInteger(EffPropString) then
        EffProp := StrToFloat(EffPropString)/10;
  end;

procedure HideModeRadiogroup;
begin
  BISCLANMainForm.rgMode.Visible := False;
  BISCLANMainForm.rgMode.Enabled := False;
  BISCLANMainForm.rbMonitorOnly.Visible := False;
  BISCLANMainForm.rbManual.Visible := False;
  BISCLANMainForm.rbInduction.Visible := False;
```

```
  BISCLANMainForm.rbMaintenance.Visible := False;
end;

Procedure ShowModeRadioGroup;
begin
  with BISCLANMainForm do
    begin
      rgMode.Visible := True;
      rgMode.Enabled := True;
      rbMonitorOnly.Visible := True;
      rbManual.Visible := True;
      rbInduction.Visible := True;
      rbMaintenance.Visible := True;
    end;
end;

procedure TBISCLANMainForm.rbManualClick(Sender: TObject);
begin
if RunMode = Manual then HideModeRadioGroup else
  if MessageDlg('Are you sure you want to change to manual mode?',
           mtConfirmation, [mbYes, mbNo], 0) = mrYes then
    begin
//    Switch off updates and stop waiting for answer from BIS monitor
      EEGMonitor.StopUpdates;
      OKtoContinue := False;
//    Set Trgt Propofol to 1mcg/ml
      ManBldPropEdit.Text := '1000';
      TrgtBloodProp := 1;
      if not GrasebySerialComm.Active then
            GrasebySerialComm.Active := True;
      Sleep(500);
      if GetCalcBloodPropConc then
        begin
          RunMode := Manual;
          StatusBar2.Panels[0].Text := 'Manual';
          IntervalTimer.Enabled := True;
          SetUpControlScreen
        end
          else
            begin
              ShowMessage('Sorry, there is a problem with the Graseby
               connection. Manual control is not currently
              possible.');
                if Sender = rbMonitorOnly then
                    rbMonitorOnly.checked := True;
                HideModeRadiogroup;
              end;
      OKtoCOntinue := True;
    end
//  If user doesn't want to change to manual mode
    else HideModeRadioGroup;
end;

procedure TBISCLANMainForm.rbMonitorOnlyClick(Sender: TObject);
begin
  if RunMode = MonitorOnly then HideModeRadiogroup
    else
    if MessageDlg('Are you sure you want to change to Monitor Only
            mode?', mtConfirmation, [mbYes, mbNo], 0) = mrYes then
      begin
        RunMode := MonitorOnly;
```

```
        IntervalTimer.Enabled := True;
        StatusBar2.Panels[0].Text := 'Monitor only';
        SetUpControlScreen;
      end
        else HideModeRadiogroup;
end;

procedure TBISCLANMainForm.sbtnDecBISTrgtClick(Sender: TObject);
  var
    temp: Integer;
begin
  temp := StrToInt(BISTrgtEdit.Text);
  if Sender = sbtnDecBISTrgt then
    if temp > 1 then temp := temp - 1;
  if Sender = sbtnIncBISTrgt then
    if temp < 100 then temp := temp + 1;
  BISTrgtEdit.Text := IntToStr(temp);
  BISTrgt := temp;
  ControlAlgorithm.SetContParmTrgt(BISTrgt);
end;

procedure TBISCLANMainForm.sbtnDecMinPropClick(Sender: TObject);
  var
    temp: Integer;
begin
    temp := StrToInt(MinPropEdit.Text);
    if Sender = sbtnDecMinProp then if temp > 99 then
      temp := temp - 100;
    if Sender = sbtnIncMinProp then if temp < 14001 then
      temp := temp + 100;
    MinTrgtProp := temp/1000;
    MinPropEdit.Text := IntToStr(temp);
    ControlAlgorithm.SetMinTrgtProp(MinTrgtProp);
end;

procedure TBISCLANMainForm.sbtnDecManBldPropClick(Sender: TObject);
  var
    temp: Integer;
begin
  temp := StrToInt(ManBldPropEdit.Text);
  if Sender = sbtnDecManBldProp then if temp >= 100 then temp := temp
- 100;
  if Sender = sbtnIncManBldProp then temp := temp + 100;
  ManBldPropEdit.Text := IntToStr(temp);
  TrgtBloodProp := temp/1000;
end;

procedure TBISCLANMainForm.sbtnDecBISVarClick(Sender: TObject);
  var
    Temp: Integer;
begin
  Temp := StrToInt(BISVarEdit.Text);
  if Sender = sbtnDecBISVar then Temp := Temp - 1
    else  Temp := Temp + 1;
  BISVar := Temp;
  ControlAlgorithm.SetVariance(BISVar);
  BISVarEdit.Text := IntToStr(BISVar);
end;

Procedure InitialiseCLANVars;
begin
```

```
  BISTrgt := StrToInt(BISCLANMainForm.BISTrgtEdit.Text);
  ControlAlgorithm.SetContParmTrgt(BISTrgt);
  BISVar := StrToInt(BISCLANMainForm.BISVarEdit.Text);
  ControlAlgorithm.SetVariance(BISVar);
  MinTrgtProp := StrToInt(BISCLANMainForm.MinPropEdit.Text)/1000;
  ControlAlgorithm.SetMinTrgtProp(Round(MinTrgtProp));
end;

Procedure SetUpControlScreen;
begin
  SetControlsStatus;
  HideModeRadiogroup;
end;

Procedure SetControlsStatus;
  var
    Auto, ManControl : boolean;
begin
  Auto := False;
  ManControl := False;
  if ((RunMode = Maintenance) or (RunMode = Induction)) then
      Auto := True;
  if RunMode = Manual then ManControl := True;
  with BISCLANMainForm do
    begin
      sbtnDecBISTrgt.Enabled := Auto;
      sbtnIncBISTrgt.Enabled := Auto;
      BISTrgtEdit.Enabled := Auto;
      sbtnDecMinProp.Enabled := Auto;
      sbtnDecBISVar.Enabled := Auto;
      sbtnIncBISVar.Enabled := Auto;
      BISVarEdit.Enabled := Auto;
      sbtnIncMinProp.Enabled := Auto;
      MinPropEdit.Enabled := Auto;
      sbtnDecManBldProp.Enabled := ManControl;
      sbtnIncManBldProp.Enabled := ManControl;
      ManBldPropEdit.enabled := ManControl;
    end;
end;

procedure TBISCLANMainForm.BISTrgtEditDblClick(Sender: TObject);
begin
  if not TonyExtras.MathsStuff.VerifyInteger(BISTrgtEdit.Text) then
    begin
     MessageDlg('Please enter an integer value', mtWarning, [mbOK],
0);
     BISTrgtEdit.Text := IntToStr(BISTrgt);
    end
    else
      begin
        BISTrgt := StrToInt(BISTrgtEdit.Text);
        ControlAlgorithm.SetContParmTrgt(BISTrgt);
      end;
end;

procedure TBISCLANMainForm.BISVarEditDblClick(Sender: TObject);
begin
  if not TonyExtras.MathsStuff.VerifyInteger(BISVarEdit.Text) then
    begin
     MessageDlg('Please enter an integer value', mtWarning, [mbOK],
0);
```

```
      BISVarEdit.Text := IntToStr(BISVar);
    end
    else
      begin
        BISVar := StrToInt(BISVarEdit.Text);
        ControlAlgorithm.SetVariance(BISVar);
      end;
end;

procedure TBISCLANMainForm.MinPropEditDblClick(Sender: TObject);
begin
  if not TonyExtras.MathsStuff.VerifyInteger(MinPropEdit.Text) then
    begin
     MessageDlg('Please enter an integer value', mtWarning, [mbOK],
0);
     MinPropEdit.Text := IntToStr(Round(MinTrgtProp*1000));
    end
    else
      begin
        MinTrgtProp := (StrToInt(MinPropEdit.Text))/1000;
        ControlAlgorithm.SetMinTrgtProp(MinTrgtProp);
      end;
end;

procedure TBISCLANMainForm.ManBldPropEditDblClick(Sender: TObject);
begin
  if not TonyExtras.MathsStuff.VerifyInteger(ManBldPropEdit.Text) then
    begin
     MessageDlg('Please enter an integer value', mtWarning, [mbOK],
0);
     ManBldPropEdit.Text := IntToStr(Round(TrgtBloodProp*1000));
    end
    else TrgtBloodProp := StrToInt(ManBldPropEdit.Text)/1000;
end;

procedure TBISCLANMainForm.rgModeClick(Sender: TObject);
begin
  HideModeRadioGroup;
end;

procedure TBISCLANMainForm.rbInductionClick(Sender: TObject);
begin
  if RunMode = Induction then HideModeRadioGroup else
    begin
      if MessageDlg('Are you sure you want to change to induction
            mode?',
        mtConfirmation, [mbYes, mbNo], 0) = mrYes then
          begin
            EEGMonitor.StopUpdates;
            if not GrasebySerialComm.Active then
                  GrasebySerialComm.Active := True;
            if GetCalcBloodPropConc then
              begin
                RunMode := Induction;
                if not Assigned(ControlAlgorithm) then
                  ControlAlgorithm := TControlAlg.Create(self,
                        ASAStatus);
                InitialiseCLANVars;
                SetUpControlScreen;
                IntervalTimer.Enabled := True;
                StatusBar2.panels[0].Text := 'Maintenance';
```

```
                end
              else ShowMessage('Sorry, there is a problem with the
                   Graseby connection. Closed loop control is not
                   currently possible.');
            end
              else HideModeRadioGroup;
    end;
end;
end.
```

Appendix 4: source code for unit EEGMonitorControl

```
unit EEGMonitorControl;

interface

uses
Windows, Messages, SysUtils, Classes, Graphics, Controls, Forms,
Dialogs, Serial3, TonyExtras;

type
  TAspectStatus = (WaitingForVersion, WaitingForHeader1,
      WaitingForHeader2, WaitingForData, CommsProb, Idle,
      SwitchingUpdatesOff, SwitchingErrorLogOff,
      WaitingForControlString);
  TEEGMonitorContrForm = class(TForm)
  BISSerialComms: TSerial;
  function CheckString: boolean;
  procedure BISSerialCommsRxData(Sender: TObject);
  procedure BISSerialCommsMessage(Sender: TObject; RxMessage: String);
  procedure SetRxChars(Status: TAspectStatus);

    private
    public
    end;

  TEEGMonitor = class(TObject)
    public
    private
    published
      procedure StopUpdates;
      Procedure SendInstruction(const Instruction: Char);
      Function TestMonitorComms: boolean;
      procedure AwaitMonitorReply;
      procedure ClearSerialPortQueues;
      Function GetNextDataString: String;
    function TestA1000Comms: boolean;
    function TestA2000Comms: boolean;
    procedure TrimDate;

const
    SecsPerDay = 60*60*24;

var
  EEGMonitor : TEEGMonitor;
  EEGMonitorContrForm: TEEGMonitorContrForm;
  AspectDataValid, AspectDataReceived, AspectConnectionOK: Boolean;
  BISValid: Boolean;
  MonitorType, NextString, AspectCtrlStr: String;
  AspectStatus : TAspectStatus;
  BaseTime, TimeAspectInstructionSent, CurrentTime, TimePrevBIS,
            TimeCurrBIS: TDateTime;
  MonitorReplied, ReplyCorrectLength: boolean;
  BIS, SR, NewBIS : Integer;

implementation

uses BISCLANMainUnit;

{$R *.DFM}
```

```
procedure TEEGMonitorContrForm.BISSerialCommsRxData(Sender: TObject);
  var
    In_String : String;
  begin
    While BISSerialComms.ReadString(In_String) > 0 do
      NextString := NextString + In_String;
    MonitorReplied := True;
    BISLoggerMainForm.StatusBar2.Panels[2].Text := 'Aspect data
      received';
  end;

function TEEGMonitorContrForm.CheckString: boolean;
  var
    StringLength: Integer;
begin
  Result := False;
  StringLength := Length(NextString);
  if MonitorType = 'A1000' then
    if ((NextString[1] = '/') and (NextString[StringLength] = #$A))
      then Result := True
      else exit;
  if MonitorType = 'A2000' then
    if ((NextString[1] = '/') and (NextString[StringLength] = #0))
then
      Result := True
      else exit;
end;

Procedure TEEGMonitor.SendInstruction(const Instruction: Char);
  begin
//  Set current time
    TimeAspectInstructionSent := Time;
    EEGMonitorContrForm.BISSerialComms.WriteChar(Instruction);
    Case Instruction of
      'V':
           BISLoggerMainForm.StatusBar2.Panels[1].Text := 'Testing';
      'D':
           BISLoggerMainForm.StatusBar2.Panels[1].Text := 'Update
            requested';
      'U':
           BISLoggerMainForm.StatusBar2.Panels[1].Text := 'Update
            requested';
      'e':
          BISLoggerMainForm.StatusBar2.Panels[1].Text := 'Error log
            off';
      'C':
          BISLoggerMainForm.StatusBar2.Panels[1].Text := 'Updates
off';
      'z':
          BISLoggerMainForm.StatusBar2.Panels[1].Text := 'Error log
            off';
      end;
end;

Procedure TEEGMonitor.AwaitMonitorReply;
  var
    Count : Integer;
begin
  Count := 0;
  BaseTime := Time;
  Repeat
```

```
    if not BISCLANMainUnit.OKtoContinue then exit
    else
    begin
      BISLoggerMainForm.StatusBar2.Panels[2].Text := 'Waiting for
            data';
      Application.ProcessMessages;
      if not BISCLANMainUnit.OKtoContinue then exit;
      if TonyExtras.TimeCalc.CalcTimeElapsed(BaseTime) > 5/SecsPerDay
            then
        begin
          BaseTime := Time;
          Count := Count + 1;
          BISLoggerMainForm.StatusBar2.Panels[2].Text := 'Aspect reply
            delayed';
        end;
      if Count = 2 then
        begin
          BISLoggerMainForm.StatusBar2.Panels[2].Text := 'Aspect time
            out problem';
          Exit;
        end;
    end;
  Until Length(NextString) > 1;
end;

procedure TEEGMonitor.ClearSerialPortQueues;
  begin
    EEGMOnitorContrForm.BISSerialComms.ZapTxQueue;
    EEGMOnitorContrForm.BISSerialComms.ZapRxQueue;
  end;

function TEEGMonitor.TestMonitorComms: boolean;
begin
  Result := False;
  if MonitorType = 'A2000' then
      if TestA2000Comms = True then Result := True;
  if MonitorType = 'A1000' then
      if TestA1000Comms = True then Result := True;
end;

procedure TEEGMonitor.StopUpdates;
begin
  SendInstruction('C');
  AspectStatus := SwitchingUpdatesOff;
end;

procedure TEEGMonitorContrForm.SetRxChars(Status: TAspectStatus);
begin
  with EEGMonitorContrForm.BISSerialComms do
    begin
    if Status = WaitingForVersion then
      begin
        MessageStartChar := 'V';
        MessageEndChar := #0;
      end;
    if Status = WaitingForHeader1 then
      begin
        MessageStartChar := 'S';
        MessageEndChar := #$A;
      end;
    if Status = WaitingForHeader2 then
```

```
      begin
        MessageStartChar := 'S';
        MessageEndChar := #0;
      end;
    if Status = WaitingForData then
      begin
        MessageStartChar := '/';
        if MonitorType = 'A1000' then MessageEndChar := #$A
          else MessageEndChar := #0;
      end;
    if Status = SwitchingUpdatesOff then
      begin
        if MonitorType = 'A1000' then
          begin
            MessageStartChar := '+';
            MessageEndChar := #$A;
          end
          else
            begin
              MessageStartChar := '/';
              MessageEndChar := #0;
            end;
      end;
    if ((Status = SwitchingErrorLogOff) or (Status =
          WaitingForControlString)) then
      if MonitorType = 'A1000' then
        begin
          MessageStartChar := '-';
          MessageEndChar := #$A;
        end;
      end;
end;

function TestA1000Comms: boolean;
begin
  Result := False;
    begin
      MonitorReplied := False;
      AspectStatus := SwitchingUpdatesOff;
      EEGMonitorContrForm.SetRxChars(AspectStatus);
      EEGMonitor.StopUpdates;
      Application.ProcessMessages;
      EEGMonitor.AwaitMonitorReply;
      if MonitorReplied = False then exit;
      AspectStatus := SwitchingErrorLogOff;
      EEGMonitorContrForm.SetRxChars(AspectStatus);
      EEGMonitor.SendInstruction('e');
      Application.ProcessMessages;
      EEGMonitor.AwaitMonitorReply;
      if MonitorReplied = False then exit;
    end;
  Result := True;
  BISLoggerMainForm.StatusBar1.Panels[2].Text := 'Aspect Comms OK';
  AspectStatus := Idle;
end;

function TestA2000Comms: boolean;
begin
  Result := False;
    begin
      MonitorReplied := False;
```

```
      EEGMonitor.StopUpdates;
      Application.ProcessMessages;
      AspectStatus := WaitingForVersion;
      EEGMonitorContrForm.SetRxChars(AspectStatus);
      EEGMonitor.SendInstruction('V');
      Application.ProcessMessages;
      EEGMonitor.AwaitMonitorReply;
      if MonitorReplied = False then exit
    end;
  Result := True;
  BISLoggerMainForm.StatusBar1.Panels[2].Text := 'Aspect Comms OK';
  AspectStatus := Idle;
end;


procedure TEEGMonitorContrForm.BISSerialCommsMessage(Sender: TObject;
  RxMessage: String);
begin
  NextString := RxMessage;
  MonitorReplied := True;
end;

Procedure TrimNull;
begin
  Delete(NextString, Length(NextString), 1);
end;

procedure TrimDate;
begin
  Delete(NextString, 1, 6);
end;

function TEEGMonitor.GetNextDataString: String;
begin
  NextString := '';
  if MonitorType = 'A1000' then
    begin
      AspectStatus := WaitingForControlString;
      EEGMonitorContrForm.SetRxChars(AspectStatus);
      SendInstruction('U');
      AwaitMonitorReply;
      NextString := '';
      AspectStatus := WaitingForData;
      EEGMonitorContrForm.SetRxChars(AspectStatus);
    end
    else
      if MonitorType = 'A2000' then
        begin
          AspectStatus := WaitingForHeader1;
          EEGMonitorContrForm.SetRxChars(AspectStatus);
          SendInstruction('D');
          AwaitMonitorReply;
          Application.ProcessMessages;
          NextString := '';
          AspectStatus := WaitingForHeader2;
          EEGMonitorContrForm.SetRxChars(AspectStatus);
          AwaitMonitorReply;
          NextString := '';
          AspectStatus := WaitingForData;
          EEGMonitorContrForm.SetRxChars(AspectStatus);
        end;
```

```
  Application.ProcessMessages;
  AwaitMonitorReply;
  StopUpdates;
  AspectStatus := Idle;
  if MonitorType = 'A2000' then
    begin
      TrimDate;
      TrimNull;
    end
    else Delete(NextString, 1, 4);
  GetNextDataString := NextString;
end;
end.
```

Appendix 5: source code for StartUnit

```
unit StartUnit;

interface

uses
  Windows, Messages, SysUtils, Classes, Graphics, Controls, Forms,
Dialogs,
  ExtCtrls, ComCtrls, StdCtrls, Buttons, BISCLANMainUnit,
EEGMonitorControl,
  TonyExtras;

type
  TStartForm = class(TForm)
    PnlInitialPanel: TPanel;
    lblInitialPanelCaption: TLabel;
    GroupBox1: TGroupBox;
    lblFirstName: TLabel;
    Label1: TLabel;
    lblSurname: TLabel;
    FirstNameEdit: TEdit;
    ASAEdit: TEdit;
    SurnameEdit: TEdit;
    bbtnContinue: TBitBtn;
    bbtnClose: TBitBtn;
    rgSaveToDisk: TRadioGroup;
    cbWriteBISToDisk: TCheckBox;
    GroupBox2: TGroupBox;
    lblEEGPort: TLabel;
    BISCommPortEdit: TEdit;
    RadioGroup1: TRadioGroup;
    LogIntervalEdit: TEdit;
    UpDown1: TUpDown;
    SaveDialog: TSaveDialog;
    rgMonitor: TRadioGroup;
    rbA1000: TRadioButton;
    rbA2000: TRadioButton;
    Edit1: TEdit;
    Label2: TLabel;
    procedure bbtnContinueClick(Sender: TObject);
    function OpenBISDataFile: boolean;
    function CloseCurrentFile: boolean;
    procedure SetPatientName;
    Function SetLogInterval: boolean;
    procedure bbtnCloseClick(Sender: TObject);
    procedure SetMonitor;
    procedure SetASAStatus;

  private
    { Private declarations }
  public
    { Public declarations }
  end;

var
  StartForm: TStartForm;
  LogInterval: Integer;
  BISDataFile: TextFile;
  PatientName: String;
```

```
  BISDataFileOpen, CommsOK, SettingUpComms: boolean;


implementation

{$R *.DFM}


procedure SetPortNumber;
  var
    PortNo: String;
begin
  PortNo := StartForm.BISCommPortEdit.Text;
  EEGMonitorContrForm.BISSerialComms.Port := StrToInt(PortNo);
end;


Procedure SetUpBISComms;
begin
  SettingUpComms := True;
  SetPortNumber;
  EEGMonitorContrForm.BISSerialComms.Active := True;
  if EEGMonitor.TestMonitorComms then CommsOK := True else CommsOK :=
      False;
  SettingUpComms := False;
end;

function TStartForm.CloseCurrentFile: boolean;
begin
  if MessageDlg('A file is still open. OK to close it? If not, new
data'
     + 'will be appended onto it?', mtConfirmation, [mbOK, mbCancel],
0) =
      mrOK then
    begin
      CloseFile(BISDataFile);
      BISDataFileOpen := False;
      Result := True;
    end
      else Result := False;
end;

function TStartForm.OpenBISDataFile: boolean;
begin
  if BISDataFileOpen = True then
    if CloseCurrentFile = False then exit;
  SaveDialog.FileName := PatientName + '1';
  if SaveDialog.Execute then
    begin
      if  FileExists(SaveDialog.FileName) then
        begin
          if MessageDlg('File already exists. OK to overwrite?',
                mtConfirmation, [mbOK, mbCancel], 0) = mrCancel then
            begin
              Result := False;
              exit;
            end;
          end;
      AssignFile(BISDataFile, SaveDialog.FileName);
      Rewrite(BISDataFile);
      BISDataFileOpen := True;
```

```
      Result := True;
    end
    else
      begin
        BISDataFileOpen := False;
        Result := False;
      end;
end;

procedure TStartForm.SetPatientName;
begin
  PatientName := SurnameEdit.Text;
  BISLoggerMainForm.Caption := PatientName;
end;

Function TStartForm.SetLogInterval: boolean;
begin
  try LogInterval := StrToInt(LogIntervalEdit.Text);
    except on EConvertError do
      begin
        Result := False;
        MessageDlg('Please enter a value above 5 (secs) for logging
            interval',
          mtInformation, [mbOK],0);
        exit;
      end;
    end;
  if LogInterval >= 5 then
    begin
      BISLoggerMainForm.SaveToDiskTimer.Interval := (LogInterval *
1000);
      Result := True;
    end
    else
      begin
        MessageDlg('Please enter a value above 5 (secs) for logging
interval',
          mtInformation, [mbOK],0);
        Result := False;
      end;
end;

Function AskIfConnected: boolean;
begin
  if MessageDlg('Is the PC properly connected to the Aspect monitor',
   mtConfirmation, [mbYes, mbNo],0) = mrNo then
     Result := False
     else Result := True;
end;

procedure TStartForm.bbtnContinueClick(Sender: TObject);
begin
    SetMonitor;
    SetASAStatus;
    if not AskIfConnected then exit;
    bbtnClose.Enabled := True;
    Application.ProcessMessages;
    if not SetLogInterval then exit;
    BISCLANMainUnit.OKtoContinue := True;
    SetUpBISComms;
    if CommsOK = False then exit;
```

```
    SetPatientName;
    if (cbWriteBISToDisk.checked = True) then
      if OpenBISDataFile = False then exit;
    StartForm.Hide;
    BISLoggerMainForm.Show;
  end;

procedure TStartForm.bbtnCloseClick(Sender: TObject);
begin
  if SettingUpComms then MessageDlg('Program will shut in 10
seconds.', mtConfirmation, [mbOK], 0);
  if BISDataFileOpen then CloseFile(BISDataFile);
  StartForm.Close;
end;

procedure TStartForm.SetMonitor;
begin
  if rbA1000.Checked then
      begin
        BISCLANMainUnit.BISMonitor := 'A1000';
        EEGMonitorControl.MonitorType := 'A1000';
      end
    else
      begin
        BISCLANMainUnit.BISMonitor := 'A2000';
        EEGMonitorControl.MonitorType := 'A2000';
      end;
end;

Procedure TStartForm.SetASAStatus;
  var
    temp : String;
begin
  temp := ASAEdit.Text;
  if TonyExtras.MathsStuff.VerifyInteger(temp) then
    if StrToInt(temp) < 4 then BISCLANMainUnit.ASAStatus :=
StrToInt(temp);
end;

end.
```

Appendix 6: source code for unit TonyExtras

```
unit TonyExtras;


interface

uses
  SysUtils;


Type
  TTimeCalc = class(TObject)
    published
      function CalcTimeElapsed(BaseTime:TDateTime): TDateTime;
    end;
   TMathsStuff = class(TObject)
     published
       function VerifyInteger(IntStr: String): boolean;
      end;
var
  TimeCalc: TTimeCalc;
  MathsStuff: TMathsStuff;

implementation

function TMathsStuff.VerifyInteger(IntStr: String): boolean;
  const
    OKChars = ['0','1','2','3','4','5','6','7','8','9', ' '];
  var
    Index: integer;
begin
  if Length(IntStr) < 1 then VerifyInteger := False
    else
      For Index := 1 to Length(IntStr) do
        begin
          If IntStr[Index] in OKChars then VerifyInteger := True
            else
              begin
                VerifyInteger := False;
                exit;
              end;
        end;
end;

Function TTimeCalc.CalcTimeElapsed(BaseTime:TDateTime): TDateTime;
  var
    CurrentTime: TDateTime;
  begin
    CurrentTime := Time;
    CalcTimeElapsed := CurrentTime - BaseTime;
  end;

end.
```

Appendix 7: source code for effect-site steering

A new function called "AdjustBloodPropTrgt" was added to the unit "Controlalg.pas". The code for this function, which implemented effect-site steering, is shown below:

```
Function TControlAlg.AdjustBloodPropTrgt(CalcBloodProp, EffProp:
single): single;
  begin
    If (((EffProp >= CalcBloodProp) and (SumDeltaTrgtProp >= 0))
        or ((EffProp <= CalcBloodProp) and (SumDeltaTrgtProp <= 0)))
            then
      TrgtBloodProp := EffProp + SumDeltaTrgtProp
      else
        TrgtBloodProp := CalcBloodProp + SumDeltaTrgtProp;
    Result := TrgtBloodProp;
  end;
```

The above function is called by the following line of code inserted into the function "CalcTrgtPropofol" (the main function of "ControlAlg"):

TrgtBloodProp := AdjustBloodPropTrgt(CalcBloodProp, EffProp);