Integrated Anaesthesia Software: Data Acquisition, Controlled Infusion Schemes and Intelligent Alarms

Nadja Mench Bressan

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Supervisor: Doctor Catarina Sofia Costa
Nunes Duarte
Position: Lecturer
Institution: King's College London.
Co-Supervisor: Doctor António Paulo Moreira
Position: Lecturer
Institution: University of Porto

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Abstract

The main contribution of this thesis is the development of a Supervisory Control and Data Acquisition (SCADA) system for using in clinical anaesthesia practice. This system, named Anesthesia Synchronization Software (ASYS), uses Target Controlled Infusion (TCI) technique. To the author's knowledge this is the first SCADA for anesthesia. The industrial concept of a SCADA was applied to a computer-aid for anaesthesia; it also incorporates intelligent alarms designed using neural networks. Physiological variables related with estimated concentrations of the drugs, provide a real time advisory system to the physician.

The second contribution of this thesis is a novel Infusion Rate Control Algorithm (IRCA). The TCI technique is mainly based on two algorithms: the Pharmacokinetics/Pharmacodynamics (PK/PD) model, and the IRCA. The novel IRCA uses a control strategy based on Optimal Control which simplifies and optimizes the computational performance of TCI.

Tests were done to assess the performance of the PK/PD models, the IRCA and ASYS as a full system. The PK/PD models showed excellent performance when compared to commercial systems. The IRCA was assessed using a standard set of tests to evaluate the novel controller; it presented a reliable and accurate performance to administer anesthesia. ASYS was developed with several functions, communicating with a total of 12 devices, namely cerebral and hemodynamics monitors, a vital signs modular monitor and infusion pumps. ASYS is being used for data acquisition in animal

research and clinically in humans. A final version of ASYS incorporating intelligent alarms is ready for the administration and control anesthesia in a clinical setting in humans.

Modern anesthesia emphasizes patient safety and outcome. Administering the right amount of anesthesia is critical, since excessive or insufficiency anesthesia cause site effects on different organs and may damage the brain to the point of causing cognitive dysfunction and increased mortality.

A SCADA for anesthesia combines informations from different monitors, allows control of drug delivery and brings together all this information to produce intelligent alarms; this may result in facilitated and improved medical care and allow increased safety and better outcome.

Resumo

A principal contribuição desta tese é o desenvolvimento de uma aplicação informática, tecnicamente conhecida por "Supervisory Control and Data Acquisition" (SCADA), para utilização na anestesia sob a técnica de Infusão Alvo Controlada (TCI), denominado Anaesthesia Synchronization Software (ASYS). Do conhecimento do autor, esse é o primeiro SCADA para anestesia.

O conceito industrial de SCADA foi aplicado numa aplicação informática para anestesia assistida por computador integrando alarmes inteligentes desenvolvidos utilizando redes neuronais. Variáveis fisiológicas relacionadas com as concentrações estimadas de fármacos compõem um sistema de aconcelhamento em tempo real ao médico anestesista.

A segunda contribução desta tese é o desenvolvimento de um novo controlador para Infusão Alvo Controlada (TCI). A técnica de TCI é composta basicamente por dois algoritmos: um modelo Farmacocinético/Farmacodinâmico e um algoritmo para controlo da infusão (IRCA). O novo IRCA usou uma estratégia baseada em Control Optimo. Esta contribução trouxe simplicidade optimizando a performance computacional do sistema TCI.

Para avaliação do sistema foram desenvolvidos testes para os modelos Farmacocinéticos/Farmacodinâmicos, para o novo controlador e para avaliar o sistema como um todo. Os modelos Farmacocinéticos/Farmacodinâmicos demonstraram um excelente desempenho quando comparados a sistemas comerciais. O novo controlador foi avaliado com base em testes específicos demonstrando ser preciso e fiável para utilização clínica.

ASYS foi desenvolvido com múltiplas funcionalidades. Para estas funcionalidades serem incorporadas no ASYS foram desenvolvidos módulos de comunicação com

9 equipamentos, nomeadamente monitores cerebrais e hemodinamicos, módulo de sinais vitais e bombas de infuão. ASYS é utilizado em investigação animal e clinicamente em humanos. Uma versão final incorporando alarmes inteligentes, está pronta a ser utilizada na administração e controlo da anestesia em humanos.

A anestesia moderna enfatisa a segurancça dos doentes e o "outcome" (resultado). Administrar a quantidade adequada de anestesia é essencial, uma vez que a anestesia excessiva ou insuficiente causa efeitos laterais sobre diferentes orgãos e afecta o cérebro ao ponto de causar disfunção cognitiva e aumento do índice de mortalidade.

Um SCADA para anestesia combina informação de diferentes monitores, permite controlar a administração de fármacos e combina toda esta informação para produzir alarmes inteligentes; isto pode resultar na melhoria dos cuidados médicos e permitir o aumento da segurança e melhor "outcome".

Contents

Publications

The following publications have been written during the course of the PhD.

Nadja Bressan, Pedro Amorim, Catarina Nunes, A.Paulo Moreira, Target Controlled Infusion a New Mathematical Algorithm to Control the Plasma Concentration, European Journal of Anaesthesiology, June 2010(3AP2-8), pg.48.

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Nomenclature

Abbreviations

ADDL	Additional Loading Dose Bolus
AI	Artificial Intelligence
AP	Arterial Pressure Software
ASYS	Anesthesia Synchronization Software
BET	Bolus Elimination and Transfer
BIT	Binary Digit
Bolus	Fast infusion
CACI	Computer-Assisted Continuous Infusion
CCIP	Computer-controlled infusion pumps
Cp	Plasma Concentration
Ce	Effect-Site Concentration
CLPS	Cycle Redundancy Check
CRC	C Language Integrated Production
DOA	Depth of Anesthesia
EEG	Electroencephalogram

EKG	Electrocardiography
ETCO2	End-tidal Carbon Dioxide
FDI	Fault Detection and Isolation
HDLC	High Level Data Link Control
HMI	Human-Machine Interface
HR	Heart Rate
IBW	Ideal Body Weight
IRCA	Infusion Rate Control Algorithm
LBM	Lean Body Mass
LOC	Loss of Consciousness
MAP	Mean Arterial Pressure
MMI	Man Machine Interface
NN	Neural Network
PK	Pharmacokinetics
PD	Pharmacodynamics
PE	Performance Error
O.R.	Operating Room
RBF	Radial Bias Function
ROC	Recovery of Consciousness
SpO2	Saturation of Oxygen
SDP	Software Development Process

TBW	Total Body Weight
TOF	Train-of-Four
TIVA	Total Intravenous Anesthesia
TCI	Target Controlled Infusion
TTPE	Time To Peak Effect

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Chapter 1

Understanding General Anesthesia and Infusion Systems

Gentlemen, this is no humbug - John Collins Warren (following the first successful demonstration of general anesthesia at the Massachussets General Hospital in 1846)

Introduction

The present chapter describes the state-of-the art of the subject of this thesis. The first part of the chapter provides a brief description of anesthesia, namely its different types and stages. The second part of the chapter addresses a specific intravenous anaesthetic technique, target controlled infusion, describing its main components, the pharmacokinetics and pharmacodynamics models (PK/PD) and the infusion rate control algorithm (IRCA). The chapter ends with a brief presentation of the structure of thesis, guiding the reader through the chapters that follow.

The anaesthesia description presented here provides relevant concepts, definitions and protocols to understand better the software requirements and the lack of technology in this field. The review of target controlled infusion systems provides an overview of the systems over the years and a summary of the technology necessary to implement the software.

Note: All the photos in the figures were done by the author, unless stated otherwise.

1.1 Anesthesia

The word anaesthesia comes from the Greek, where the combination of an (negative) and aisthesis (sensation), means the loss of sensation. This loss of sensation can be induced pharmacologically by means of several different anaesthetic drugs. Anaesthetics differ regarding the receptors where they act and also the route of administration. Most anesthetics produce their effect by acting on Gamma-Aminobutyric acid (GABA) N-methyl-D-Aspartic (NMDA) or opioid receptors. Routes of administration are: the airways for volatile agents (gases), the veins, that is directly into the circulatory system for drugs delivered intravenously, or locally, into a small area of the body where surgery, usually minor, is to be performed, or regionally to block sensation and motion in a larger area of the body, usually a limb y, by the administration of the so called local anesthetics to produce local or regional anesthesia [13].

General anaesthesia can be defined by four main components: unrousable unconsciousness, reflex depression, decreased or abolished muscle tone and homeostasis1.1.

Unrousable unconsciousness: A person is conscious when he/she is aware of his/herself; in contrast, unconsciousness, the loss of consciousness implies a person that cannot receive and process information coming from outside the body. If a person, for any reason, is unconscious, he or she can be rousable or unrousable depending on the concentration of anesthetic drugs in the body and the intensity of the stimulus applied.

The first step in general anaesthesia is to produce an unrousable unconsciousness and implies the administration of a so called hypnotic drug. The term hypnotic can be misleading: if one thinks of hypnosis as the induction of sleep, then one must

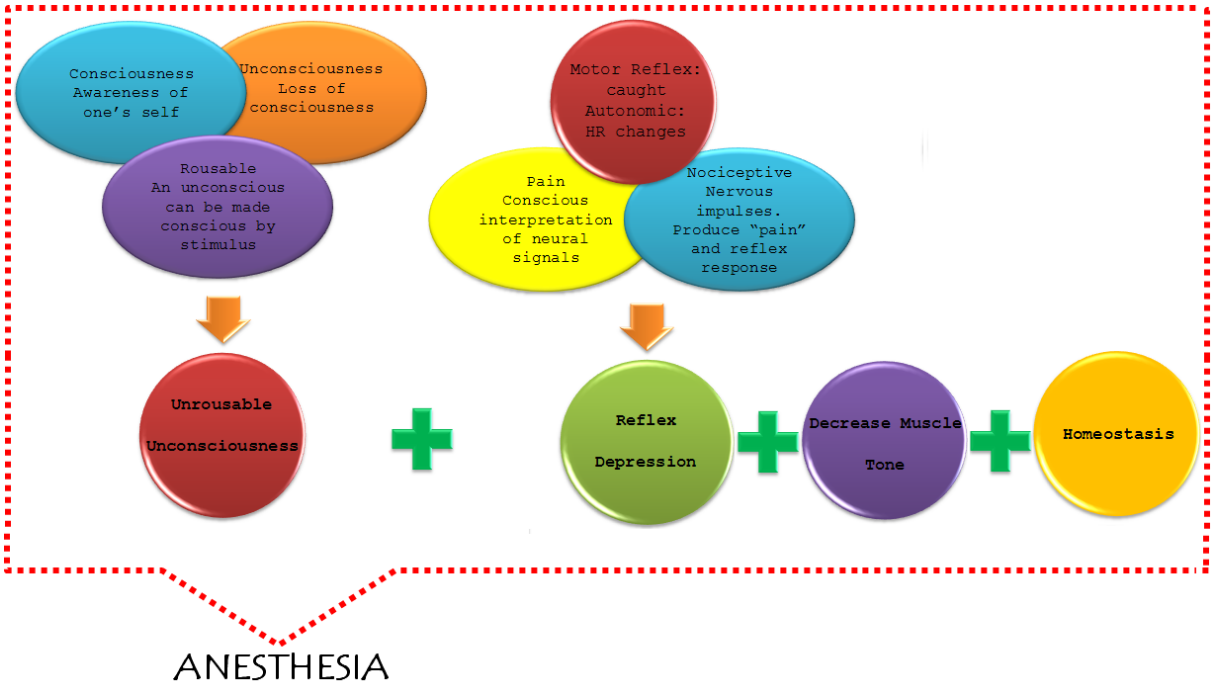

Figure 1.1: Anesthesia Structure.

bear in mind that anesthesia differs substantially from natural sleep; if one thinks of hypnosis as the stage achieved through hypnotism, than again this has nothing to do with anesthesia, since an hypnotized subject is conscious. Hypnosis achieved through the administration of anesthetic drugs is quite close to a state of coma, so that, in fact, it can be defined as a state of pharmacologically induced coma. This state is reversible, whereas coma may not be reversible.

Reflex depression: During the surgical procedure the patient will be under several stimuli (e.g., skin incision). These stimuli act on the unconsciousness subject to elicit a nociceptive response. To prevent this response, a specific anesthetic drug must be used, one with anti-nociceptive properties. Analgesics are the most commonly used drugs used to achieve that effect, with opioid analgesics being the most potent and, for that reason, the most widely used.

Decreased muscle tone: To ensure patients immobility during the operation as well as to allow endotracheal intubation, drugs that block the neuro-muscular trans-

mission are used. However, not all surgical procedures require total lack of motion; also paralysis may be not needed during the entire surgical procedure. The decrease in muscle tone should be considered a component of the patientss anesthetic care and not an integral part of general anesthesia.

Homeostasis: Maintenance of physiological functions or homeostasis is the fourth component of anaesthesia. During the period of anaesthesia, physiological functions are altered, both as a result of the side effects of the anesthetic drugs, but also as a result of the surgical procedure itself and its consequences, as the loss of blood, electrolyte and acid base changes, tissue damage, etc. Also, the respiratory system, the cardiovascular system and the nervous system are directly altered by the anesthetics, and it is essential to limit the damage produced by such changes and to ensure normal body function when the patient recovers from anaesthesia [13].

Before the administration of general anesthesia some procedures need to be carried out.The subject is prepared with an intravenous access (a plastic cannula) through which anesthetic drugs will be administered. This intravenous access is the input for drugs and for different fluids administered during anaesthesia. Extensive monitoring is an essential part of the anesthetic procedure. Monitoring starts before induction of anesthesia. Some monitoring starts only after induction of anesthesia, mainly because it requires invasive procedures. Some monitors are used only in special situations.

Cardiovascular Monitoring:

- Electrocardiography (EKG). The electrocardiogram is the recording of the electrical activity generated by the heart. These electrical impulses can be recorded through the skin by placing three or five electrodes on the chest. EKG monitoring is mandatory throughout the entire anesthetic procedure. It is used to assess heart rate, to detect arrhythmias and to evaluate cardiac abnormalities, namely

ischemia. It is incorporated in the modular monitor of physiological variables.

- Blood Pressure: During all phases of anaesthesia it is mandatory to measure the blood pressure. This is usually performed non-invasively and automatically. It is done repeatedly at a frequency determined by the status of the patient and the type of procedure. The method used is oscilotonometric, with a cuff and a manometer, using a device which is part of a modular monitor of physiological variables. Blood pressure is monitored during anaesthesia in order to avoid either hypotension (low blood pressure) or hypertension (high blood pressure). It can be also measured beat-to-beat with an intrarterial catheter and a pressure transducer. This can be done starting before induction of anesthesia.

- Other cardiovascular measurements: Blood pressure in the central circulation is also monitored, in selected cases, and always by means of catheters placed in or in the vicinity of the heart (the so called central catheters). These allow assessment of Central Venous Pressure, Pulmonary Arthery Pressure, Cardiac Output, Vascular Resistance, etc. Such variables are displayed in the modular monitor.

- Minimally invasive hemodynamics: Modern stand alone monitors use minimally invasive techniques, as opposed to the placement of central catheters, to assess Cardiac Output, Vascular Resistance and volume status of the circulation.

Respiratory Monitoring:

- Pulse Oxymetry: Inadequate ventilation or oxygenation can cause a decrease of oxygen pressure and saturation in the arterial blood (hypoxia). The pulse oxymeter is mandatory through all phases of anesthesia. It measures the degree of oxygenation of haemoglobin. A sensor placed in a thin part of the body, as the tip of a finger, allows light to cross it and measures the light absorption at two wavelengths to obtain the arterial oxygen saturation (SaO2). Hypoxia can be detected by SaO2 continuous monitoring. This oxymeter is a pulse oxymeter,

measuring the pulsatile component of light absortion and obtaining an assessment of the shape size of the pulse wave, the so called plethismography. This reading provides information about the circulation and also about nociception. The pulse oxymeter is part of the modular monitor.

- Ventilation and gases: Ventilation is continuously assessed by measurements of respiratory pressures, volumes and flows. This is mandatory during general anesthesia. The concentrations, inspired and expired, of different gases, oxygen, carbon dioxide, and anesthetic gases are also measured. These are displayed on the modular monitor.

Temperature Monitoring:

- Temperature: Usually, the body temperature is measured during anaesthesia by use of bimetallic thermometer. Both central (esophageal) or peripheral (fingertip) temperatures can be measured. Assessment of body temperature is important to detect deviations from normal temperature and to assess the circulation (dilatation of blood vessels or volume status). Temperature values are displayed on the modular monitor.

Nervous System Monitoring:

- Electroencephalogram (EEG): The EEG is a measurement of the brain electrical activity. It uses surface electrodes placed on the head. Special EEG monitors were recently developed for use in anesthesia: a sensor with several electrodes is placed on the forehead and the EEG is processed in order to obtain an numeric index which reflects the hypnotic component of anesthesia. Such monitors and indexes allow the assessment of the level of anesthesia, usually referred to as the assessment of depth of anesthesia (DOA). EEG drived indexes can be part of or displayed on the modular monitor.

- Cerebral Oxymetry: Special stand alone monitors allow the assessment of cerebral oxygenation, either globally (jugular bulb oxygen venous saturation) or regionally

(near infra-red spectroscopy). These are used in selected cases. They can be particularly helpful to discriminate between the cerebral effects of anesthestics and cerebral ischemia, which may occur as a complication of surgery and confound the overall assessment of anesthesia.

Neuromuscular Transmission:

- Neuromuscular Transmission: The efficacy of the neuromuscular transmission is affected by the administration of muscle relaxants, drugs that block the neuromuscular transmission to produce either full or partial muscle paralysis. Since even limited degrees of paralysis can impair spontaneous ventilation, monitors are used to assess neuromuscular transmission. An electrical current is applied to a peripheral nerve through skin electrodes and the response at the muscle is assessed. These monitors are incorporated in the modular monitors.

1.1.1 Phases of Anesthesia

1. Induction

   The first phase of anesthesia is induction. This is a critical phase: an analgesic, an hypnotic and a muscle relaxant have to be administered in doses high enough to produce unconsciousness and allow a very aggressive manouver, endotracheal intubation.

   Induction causes severe respiratory depression and respiratory arrest and some degree of cardiovascular depression. The rapid and potentially profound changes in cerebral, respiratory and cardiovascular functions require close monitoring of the patient and careful titration of anesthetic drugs. Due to respiratory depression and respiratory arrest caused by paralysis, mechanical ventilation is performed. The placement of a tube inside the trachea is required to allow the use of mechanical ventilation and to seal the airway (trachea). Intubation is performed

under direct vision, laringoscopy, both being very potent nociceptive stimuli.

The anaesthetic protocol, here described, uses s the Target Controlled Infusion (TCI) technique, which will be introduced later in this chapter.

The physician, with the patient monitored, starts by administering an analgesic, usually an opioid. This is required to attenuate the nociceptive responses to laringoscopy and tracheal intubation. Given the synergism between opioids and hypnotics, prior administration of an opioid reduces hypnotic requirement. Following the opioid an hypnotic drug is administered to produce unconsciousness. The drug doses of opioid and hypnotic administered depend on the expected clinical effect according to several covariates as patients weight, height, age and gender as well as to the general status of the patient.

Loss of consciousness (LOC) is defined as the moment the subject no longer responds to verbal commands (open your eyes) and to a mechanical stimulus (tapping on the forehead). Co surgery, administration of a muscle relaxant is performed too. A sensor to measure the level of neuromuscular blockade has been previously placed.

After the administration of a muscle relaxant, a standard train-of-four set of electrical stimuli are applied to a peripheral nerve and the response at the level of a muscle enervated by the stimulated nerve is observed. Once the set of four responses is abolished tracheal intubation is carried out. After intubation the endotracheal tube is connected to a ventilator and mechanical ventilation ensues.

Anesthetic drugs are titrated in order to maintain unconsciousness, reflex depression, analgesia and maximum possible stability of physiological parameters and

functions during the surgical procedure to follow. This completes the induction phase of anesthesia which usually lasts a few minutes.

Before surgery it is often necessary to insert other catheters, namely a Folley catheter to measure urine output, or other vascular catheters for fluid infusion and the measurement of invasive parameters. Assessment of cardiovascular functions is very important, namely because they reflect the action of anesthetic drugs, and also because changes due to the action of anesthetics also impend on the cerebral effect of the anesthetics themselves. The important cardiovascular changes caused by induction of anesthesia and reduction of cerebral activity are followed by more cardiovascular changes caused by the surgical procedure; this results in a highly dynamic system where the action of anesthetics is constantly changing due to changes in the state of the patient and where the state of the patient is changing due to the action of anesthetic drugs.

2. Maintenance:

   Maintenance follows induction of general anaesthesia. In this phase, the anaesthesiologist balances anaesthesia with the use of anesthetics agents and manages intravenous fluid infusion and the administration of different drugs to maintain hemodynamic stability and normal function of body organs. The control of hemodynamic, physiological, and cerebral functions is more rigorous and stressful in this phase, particularly if the surgical procedure has a duration of several hours and/or causes major tissue damage or blood loss.

3. Emergence:

   Emergence is the phase that follows the end of the surgical procedure. The goal is the full reversal of neuromuscular blockade, smooth return of spontaneous ventilation and reflexes, stability of hemodynamics and other physiological functions, so that return of consciousness (ROC) can occur in a safe and comfortable envi-

ronment.

Anesthetic drugs are titrated so that analgesia is present in order to cope with pain from the surgical wound and hypnotic drugs are stopped assuring that ROC happens in comfort. Once respiration and reflexes have returned and the patient regains consciousness, the removal of the tracheal tube (extubation) is performed.

The patient is then usually transferred to a recovery room, or post anesthesia care unit, for a few hours until complete recovery from anesthesia.

1.2 Review of Target Controlled Infusion

TCI is an anesthesia technique used mostly for intravenous anaesthesia, that makes use of two main important components: pharmacokinetics/pharmacodynamics models (PK/PD) to simulate the drug/body behaviour, and an infusion rate control algorithm (IRCA) to drive infusion devices.

1.2.1 Pharmacokinetic/Pharmacodynamic Models

The PK/PD model simulates the drug behaviour inside the body. To better understand the pharmacology of a drug, it can be divided into two phases as follows:

- PK phase:

  When a drug is administered intravenously, it goes into the blood, the so called central compartment, from where it is distributed, metabolised and excreted. Pharmacokinetics describe what the body does to the drug [14], as represented in figure 1.2:

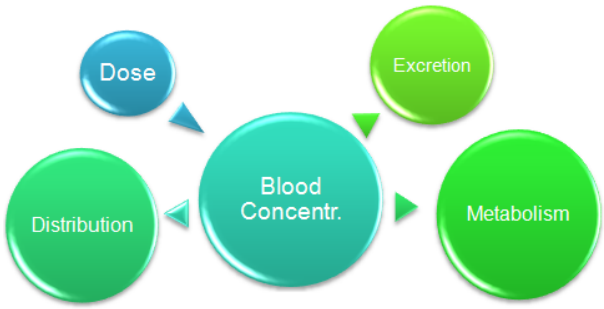

Figure 1.2: Pharmacokinetic Phase.

- PD phase:

  Part of the drug administered reaches the effect organ, that is the organ where the drug will produce the desired clinical effect . If a hypnotic was the drug given, then, the brain will be the effect-site organ. For opioids, both the brain and the spinal cord will be the effect-site. For muscle relaxants, muscles will be the effect-site.

  When the drug reaches the effect organ, it reacts with receptors at the organ producing a clinical effect. This second phase describes what the drug does to the body [14], the Pharmacodynamics as represented in figure 1.3:

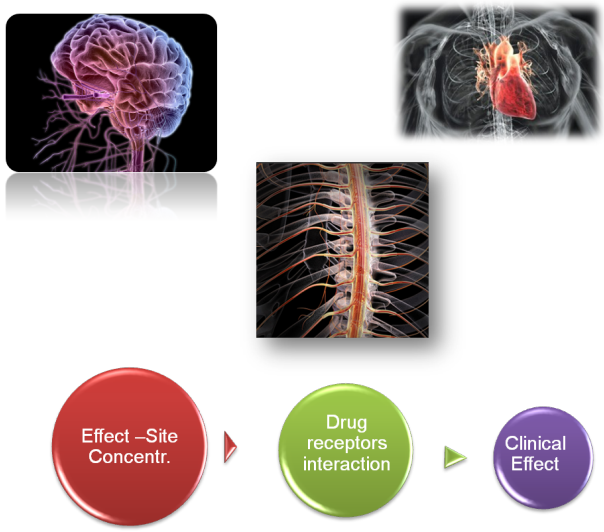

Figure 1.3: Pharmacodynamic Phase.

In the 70s the drug/body behaviours were expressed as a mathematical models to simplify understanding of these complex processes and to provide an estimation of drug concentrations in the body. This knowledge allowed physicians to improve clinical administration of drugs [15]. The first PK models were used only two compartments: V_1 as the blood compartment or central compartment and V_2 as a peripheral compartment, as shown in figure 1.4.

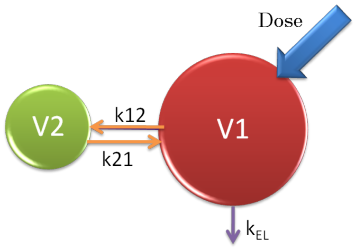

Figure 1.4: Two-compartment Model. V_1:volume 1, V_2:volume 2, k_{ij}: constant rates

However, when a drug bolus is given, and a peak occurs in the plasma concentration, one must expect a delay between this plasma peak and the resulting peak at the effect site. It is very important to know, because of its clinical implications that a delay exists between the two peaks. This delay is called hysteresis. Evidence about this delay, allowed Hull [1] to conclude that the plasma was not the site of drug effect. Considering this theory, the structure of the PK model was redesigned with one more compartment, or the so called biophase, graphically represented in figure 1.5:

Hulls first scheme of the PK model [1] was represented by three volumes, with the third being the biophase. Nowadays, for most opioids and hypnotics, the PK/PD scheme has three compartments and the biophase [16], as represented in figure 1.6:

Where the volume V_1 is considered the blood compartment or central compartment; volume 2 or second compartment V_2, the fast or vessel-rich compartment, and the volume 3 or third compartment V_3, the slow or vessel-poor compartment. The concentration in the central compartment is defined as the plasma concentration (C_p)

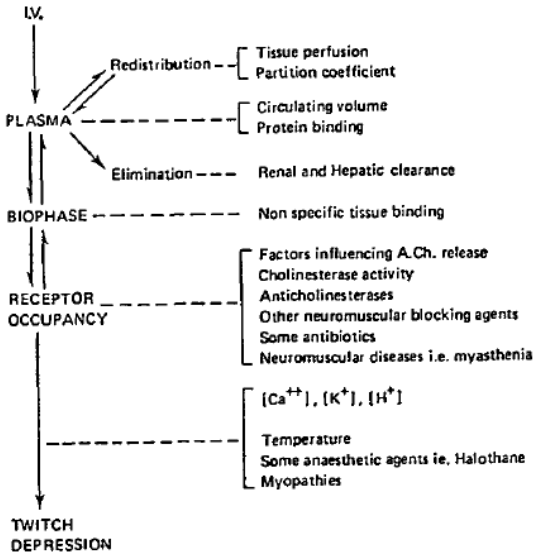

Figure 1.5: Figure adapted from the Article Pharmacokinetics and Pharmacodynamics [1].

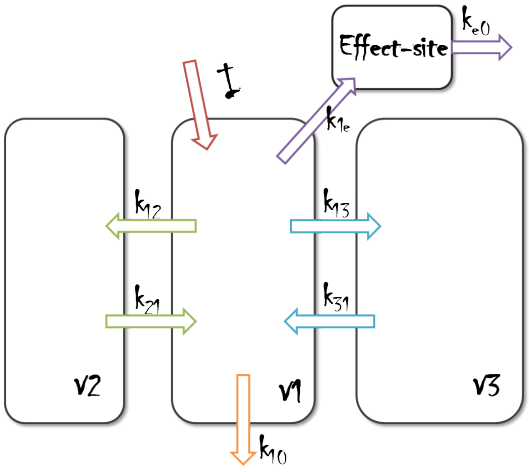

Figure 1.6: Pharmacokinetic Model. V_1:volume 1, V_2:volume 2, V_3:volume 3, k_{ij}: constant rates

[14].

When a drug dose is administered (I) into the central compartment, it is transferred to the second and the third compartments, as expressed by the rate constants represented by k_{ij}, where i and j express the transfer and elimination between compartments i and j. The rate constant k_{10} is the elimination constant of the drug

from the organism.

The PK/PD model with four compartments is also called link model, since the drug effect relates the time-course of the plasma concentration to the time-course of the drug effect. The volume of the effect-site is represented by 1/10000 of the central compartment V_1 and is linked to the central compartment by the rate constant k_{1e}. k_{1e} is considered equal to $k_{e0}/10000$, the smallest rate constant in the model. Therefore, k_{1e} is not representative of the pharmacokinetics of the drug. k_{e0} was established as a rate constant to represent the balance between the plasma and the site of drug effect, as well as the elimination constant through from effect compartment [17].

The link model, figure 1.6, can be described by the following differential equations (1.1, 1.2, 1.3, 1.4):

$$\dot{m}_1(t) = -(k_{12} + k_{13} + k_{10}) \cdot m_1(t) + k_{21} \cdot m_2(t) + k_{31} \cdot m_3(t) + I(t) \tag{1.1}$$

$$\dot{m}_2(t) = k_{12} \cdot m_1(t) - k_{21} \cdot m_2(t) \tag{1.2}$$

$$\dot{m}_3(t) = k_{13} \cdot m_1(t) - k_{31} \cdot m_3(t) \tag{1.3}$$

$$\dot{m}_4(t) = k_{1e} \cdot m_1(t) - k_{e0} \cdot m_4(t) \tag{1.4}$$

Where m_1, m_2, m_3, m_4 are the masses of the compartments: V_1, V_2, V_3, V_e; $I(t)$ the infusion rate, using Laplace Transform with zero initial conditions. The term $k_{e0}m_4(t)$ and k_{1e} were not considered in the equation 1.1, since their value are very near to zero [17]:

$$s \cdot M_1(s) = -(k_{12} + k_{13} + k_{10}) \cdot M_1(s) + k_{21} \cdot M_2(s) + k_{31} \cdot M_3(s) + I(s) \quad (1.5)$$

$$s \cdot M_2(s) = k_{12} \cdot M_1(s) - k_{21} \cdot M_2(s) \quad (1.6)$$

$$s \cdot M_3(s) = k_{13} \cdot M_1(s) - k_{31} \cdot M_3(s) \quad (1.7)$$

$$s \cdot M_4(s) = k_{1e} \cdot M_1(s) - k_{e0} \cdot M_4(s) \quad (1.8)$$

TCI can be described as an open-loop system, figure 1.7, where the drug dose is pre-programmed to achieve and maintain a desired plasma concentration without feedback from the system.

Figure 1.7: Block diagram of PK/PD Model. I drug dose; M_1 concentration.

Therefore, considering figure 1.7:

$$H(s) = \frac{M_1(s)}{I(s)} \tag{1.9}$$

$$\frac{M_1(s)}{I(s)} = \frac{s^2 + (k_{21} + k_{31}) \cdot s + k_{21} \cdot k_{31}}{s^3 + p_1 \cdot s^2 + p_2 \cdot s + p_3} \tag{1.10}$$

Where:

$$p_1 = k_{31} + k_{21} + k_{12} + k_{13} + k_{10} \tag{1.11}$$

$$p_2 = k_{21} \cdot k_{31} + k_{12} \cdot k_{13} + k_{13} \cdot k_{21} + k_{10} \cdot k_{31} + k_{10} \cdot k_{21} \tag{1.12}$$

$$p_3 = k_{21} \cdot k_{31} \cdot k_{10} \tag{1.13}$$

The plasma concentration ($C_p(t)$) is obtained by:

$$C_p(t) = \frac{M_1(t)}{V_1} \tag{1.14}$$

$$V_1 = V_c \cdot WeightPacient \tag{1.15}$$

V_c is a parameter from the PK model. If $I(t) = 0$ $t \geq 0$ the plasma concentration ($C_p(t)$) is defined in time by:

$$C(t) = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t} + C \cdot e^{-\gamma \cdot t} \tag{1.16}$$

Where A, B, C, α, β, γ are pharmacokinetics parameters and t is the time since the bolus. The effect-site concentration ($(C_e(t))$) in time is a convolution of the C_p over time with the disposition of the effect-site[18], as follows:

$$C_e(t) = C_p(t)\left(1 - e^{-k_{e0} \cdot t}\right) \tag{1.17}$$

Considering the PK/PD models, the drug dose is the input and the estimated concentration at the effect site, the output. The estimation of plasma and effect-site concentrations are based on model interaction with the drug dose [19], [20]. The input/output of the anesthesia process represents the cause-effect relationship between drug dose and the drug concentration at the specific site. As an open-loop control system, figure 1.8, TCI uses a controller and an actuator to obtain the desired response.

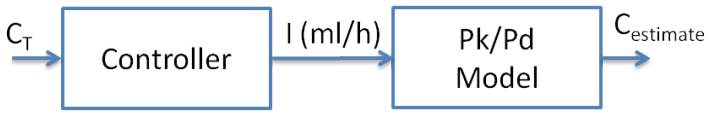

Figure 1.8: Controller and PK/PD model diagram. C_T:target concentration; $C_{estimate}$: estimated concentration.

TCI systems allow the anesthesiologist to target a drug concentration during anesthesia and remotely control an infusion device to reach and maintain the target concentration (C_T) at plasma or drug of site effect. This is done using an IRCA, as addressed ahead.

1.2.2 Infusion Rate Control Algorithm and Controllers

With the aim of producing a specific effect, the anesthesiologist establishes a desired target concentration. The PK/PD model algorithm calculates the drug amount needed

to achieve that concentration, and an infusion rate control algorithm (IRCA) determines a control strategy to administer the drug dose, figure 1.9.

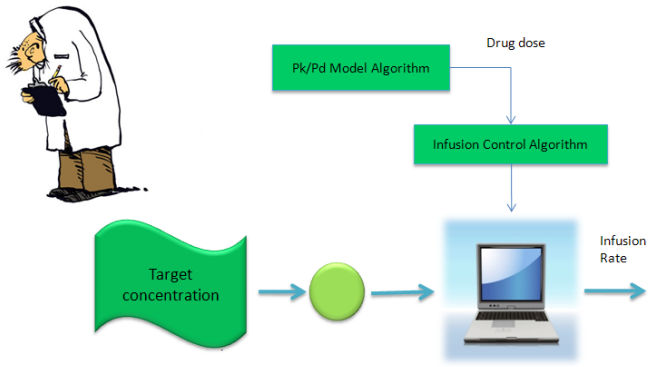

Figure 1.9: Partial diagram block of the TCI system.

Schwilden [21], one of the TCI pioneers, developed the concept or scheme used in IRCA, called bolus elimination and transfer (BET).

The BET scheme follows a vector of infusions. It starts with a fast infusion, called bolus (B) to fill the central compartment, and rapidly achieve the target concentration (C_T). This is followed by a continuous infusion composed of two parts: one to give an amount to replace the drug eliminated (E) from the central compartment and another to give an amount to replace drug transferred (T) between the peripheral compartments [14].

The structure of an IRCA relies on the BET concept, aiming at achieving rapidly the C_T without overshoot and maintaining the concentration in the target. Therefore the IRCA is limited by the BET scheme in bolus and maintenance.

One of the first TCI systems tested in a clinical trial was the computer-assisted continuous infusion (CACI) presented by Alvis [22]. The IRCA of CACI was an optimisation of the Schwilden controller [21], controlling a three-compartment model

and considering the weight of the patient for the calculation of the volume of the central compartment. In addition to the BET scheme, a sequence of three rules to control an actuator were introduced in the first controller for Cp, figure 1.10.

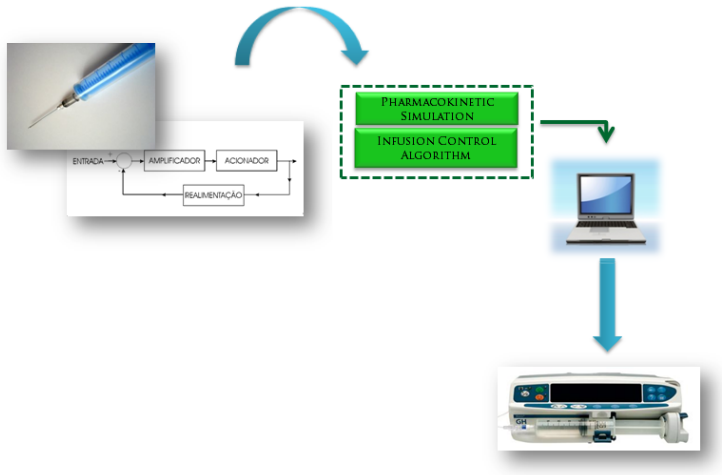

Figure 1.10: Diagram block of the IRCA.

The IRCA of the CACI system presented two equations and three rules to the infusion device, as follows:

1. Rule 1: $C_{pT} > C_p$: To increase plasma concentration from C_p to C_{pT} (new plasma concentration target), a bolus must be commanded to the infusion device to fill the central compartment, calculated by equation 3.7.

$$ADDLD = (C_{pT} - C_p) \cdot V_1 \tag{1.18}$$

   To keep the plasma concentration compensating the drug transferred between compartments and the elimination from the central compartment, a constant infusion is administered by the infusion device, calculated by equation 3.8:

$$I(t) = C_{pT} \cdot V_1 \left(k_{10} + k_{12} \cdot e^{-k_{21} \cdot t} + k_{13} \cdot e^{-k_{31} \cdot t}\right) \tag{1.19}$$

2. Rule 2: $C_{pT} = C_p$: To maintain plasma concentration at same target, the equation 3.8 is recalculated every $10s$ based on the PK model to define the amount

of drug the device delivers to the patient.

3. Rule 3: $C_{pT} < C_p$: To decrease plasma concentration the infusion device is stopped until the target concentration has been reached. The infusion device titrate a constant infusion by equation 3.8 during the maintenance.

Since the development of the IRCA of CACI system and in order to achieve a certain C_T, a drug dose must be commanded by the IRCA to the infusion device. The IRCA became a complex algorithm controlling the drug dose administered and the correct accomplishment of the command by the infusion device. Over the last 20 years, different research groups have developed variations of controllers for C_p [23], [24], [25], [26].

Considering the evolution of IRCA, the simple analytical solution presented by Bailey [27] was the most relevant algorithm to control C_p it has since been implemented in several TCI systems. Bailey improved Jacobs [26] analytical solution simplifying the control of C_p, optimizing the algorithm performance, and reducing the infusion rate to the equation 1.20:

$$I\left(t\right) = \frac{C_T - C_p\left(t + 2\Delta t\right)_{I=0}}{C_p\left(\Delta t\right)_{I=1}} \tag{1.20}$$

In equation 1.20 the term $C_T - C_p\left(t + 2\Delta t\right)_{I=0}$ represents the difference between the target concentration and the estimated concentration at $t+2\Delta t$ if $I = 0$. The term $C_p\left(\Delta t\right)_{I=1}$ represents a constant infusion or the maintenance infusion, therefore, I is the exact infusion to progress from $C_p(t + \Delta t)$ to C_T.

In his study, Bailey concluded that the plasma was not the site of effect for most of the drugs, so that the controller for effect-site concentration became a new

challenge for researchers who followed and for the work developed in the 1990s.

One of the first effect-site concentration controllers was the one published by Shafer [17]. This author used an analytical solution to approach the control of effect-site and presented an algorithm for computer-controlled infusion pumps (CCIP). In Shafers CCIP, the concept of time-to-peak effect (TTPE) was introduced as a model-independent parameter.

The TTPE is defined as the time-course between a bolus and the moment, or time point, when plasma and effect-site concentration curves cross, as shown in figure 1.11. This is the time of maximum effect-site concentration after a bolus in an empty system [14].

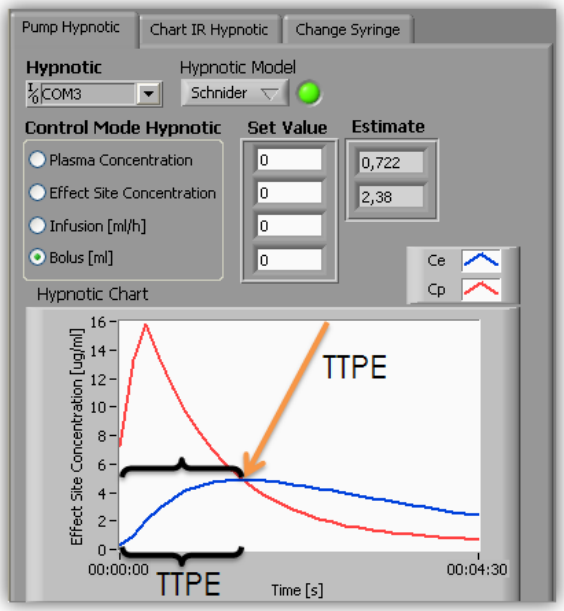

Figure 1.11: Time to peak effect, after a bolus of 5 ml using Schnider PK/PD model for a 70 kg, 170cm and 30 years old male subject.

Both solutions presented in the study used TTPE to minimize errors during real time application. The authors provided two algorithms to control C_e, rapidly achieving the target concentration and easily maintaining it over time. Given its com-

plexity, this algorithm will be described in the chapter 3. The CCIP described by Shafer is the IRCA used in several well-known TCI systems, as also described in the following section.

1.2.3 Target Controlled Infusion Systems - TCI

The TCI system is described as a technique to be used at TIVA based on PK/PD models driven an infusion device. The system is composed basically by:

(a) PK/PD: a validated model with specific parameters for anesthetic drugs;

(b) IRCA: to control the actuator - infusion device;

(c) Control unit: microprocessor or personal computer (PC);

(d) Actuator: infusion device;

(e) Communication: system between the control unit and the actuator;

(f) User Interface: also called Human-Machine Interface (HMI) receives the patients input data and targets the desired concentration

The control unit executes the algorithm with the PK/PD model and the IRCA, using the patients data and the desired C_T, previously set by the physician as shown in figure 1.12. The program compares the C_T with the estimated concentration at real time during intervals of $10s$. The microprocessor, based on the PK/PD model, calculates the drug amount needed to achieve the C_T and command the infusion device with an infusion rate. The infusion device administers the drug amount to be delivered to the subject and sends information about the the drug dose administered back to the microprocessor. The microprocessor computes the error between the drug amount commanded and the drug amount administered, and calculates the next drug amount comparing the C_T and updated estimated concentration by the PK/PD model. This

cycle is repeated every $10s$ until C_T has been achieved.

Figure 1.12: TCI system components.

The TCI system can be explained in a block diagram, where the desired concentration is the input, and the drug amount administered is the output. The control component of a TCI system, previously described as the infusion rate control algorithm, has two specific tasks. These are included to control the drug amount administered and to regulate the function of the infusion device. TCI have been described as open loop systems, however the physician acts as a feedback, increasing, decreasing or keeping the targets based on physiological, hemodynamic and cerebral variables, as graphically depicted in figure 1.13:

Coetzee [28] listed several benefits of TCI: the easiness to assess the relationship between a drugs concentration and its effect, the automatic compensation for any interruption in the infusion, the calculation of time to reach a given concentration and predict recovery and the possibility of targeting the effect-site. TCI systems are accurate, fast and trustworthy to estimate the plasma and effect-site. TCI systems have been showed to offer several advantages over manual TIVA [29].

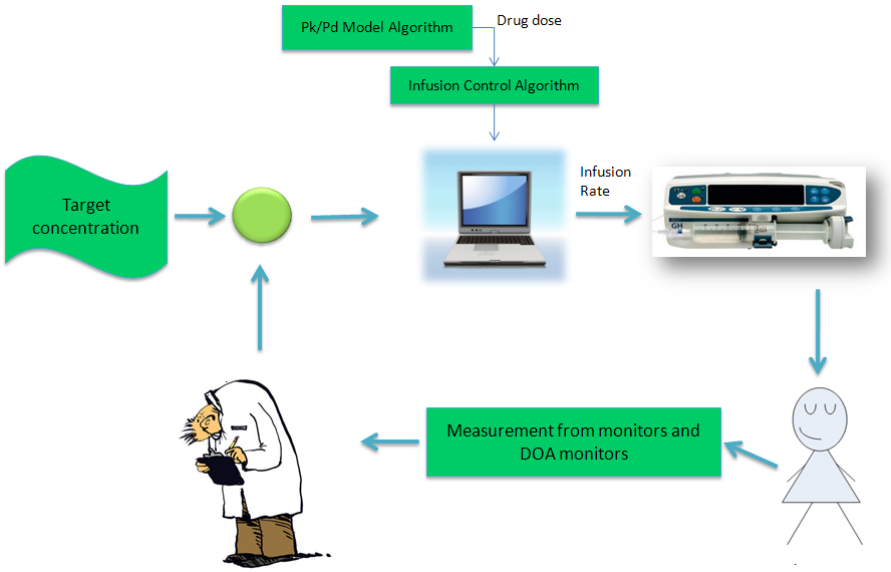

Figure 1.13: Diagram block of a TCI system.

TCI systems are currently used on a daily basis in clinical practice, mainly because of their benefits from automation; however its use still represents a very small percentage of TIVA anesthesia and TCI has not been approved for use in the USA by the FDA, so it is not available in that country.

TCI systems can control each component of anesthesia, such as hypnosis, analgesia and muscle paralysis, which can be independently regulated and adapted to changes depending on the phase of the anesthetic and surgical procedures and patients condition. These systems became very useful tools for the anesthesiologist, working both as an advisor and also as a better way to administer anesthetic drugs. Several research groups, aiming at improving TCI systems, developed different concepts and methods to optimize the technique, as follows:

1. CATIA: The BET scheme was implemented and tested in 6 subjects in the first TCI system called computer assisted total intravenous anesthesia (CATIA) by Schwilden in [21].

2. TIAC: Developed by Ausems, a computer assisted infusion pump controlled alfen-

tanil infusion has been tested in abdominal surgery. The system presented a good performance and accuracy for estimation of plasma concentration [30].

3. CACI: The computer assisted continuous infusion, developed by Alvis was written in Pascal, implemented in Apple II Plus using an infusion pump IMED 929. The system was tested in a clinical trial with 30 subjects under general anesthesia during coronary artery bypass. The CACI controlled the administration of fentanyl keeping the target plasma concentration stable and accurate [22].

4. STANPUMP: The system developed by Shafer started a new generation of TCI systems controlling the effect-site concentration. The system presented good results administering bolus and continuous infusions as well as keeping the of plasma and effect-site concentration of fentanil [17].

5. IVA-SIM: Developed by Schuttler is a simulation software using TCI technique [31].

6. RM Tackley: Developed by Tackley the system controlled propofol. The system was tested in clinical trial in 8 subjects under general anesthesia during surgery [25].

7. Target Controlled Infusion (TCI): Developed by Chaudhri and Kenny this was the software that led to the adoption of this name by the American Society of Anesthesiologists [32].

8. PKPD Tool for Excel: A didactic tool developed by Shafer in Excel spreadsheet (from Microsoft) for the simulation of PK/PD models and TCI technique [33].

9. TIVA Trainer: Simulation software developed by Frank Engbers and Nick Stucliff [34].

10. Rugloop: The most used and known TCI system, Rugloop was developed by Tom De Smet and Michel M.R.F. Struys. Rugloop, 1.14 is a research software used by several scientists around the world. Besides being a TCI device, Rugloop adds

the functionality of data acquisition and synchronization, communicating with more than 15 different devices and monitors [35].

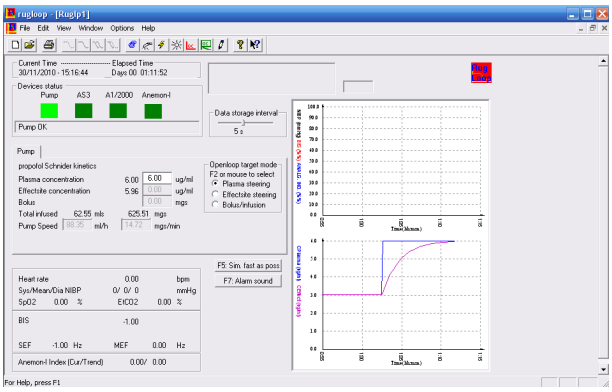

Figure 1.14: Rugloop I - Didactic Version of the TCI software.

11. Anestfusor: A programme, figure 1.15, developed in 2002 by Muñoz, Brinckmann, and Stutzin with support from GlaxoSmithKline Chile, Mediplex and Fresenius-Kabi Chile. The program communicates with six different devices and monitors [2].

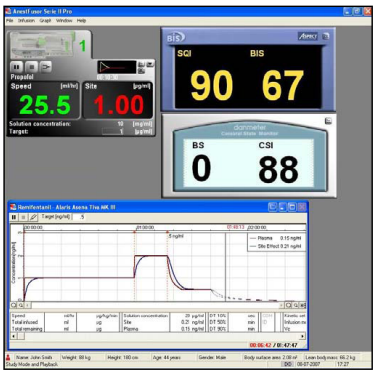

Figure 1.15: Screen of the Anestfusor TCI software [2].

12. iAssist: Developed by Cristopher Brouse, Guy Dumont, Ping Yang and Mark Ansermino. iAssist is a software for data acquisition and synchronization using artificial intelligence technique to guide the clinician during the anesthesia procedure [36].

The TCI technique has been incorporated in infusion devices with increased practicality and simplicity. TCI devices include a pre-programmed microprocessor.

Commercially available infusion devices with TCI do not collect external data from the patient; still they have become a reliable and simple tool in clinical practice.

The pioneer company to introduce a TCI device in the market was Astra Zeneca. With an algorithm developed by White and Kenny, the Diprifusor used a PK model controlling C_p, and became the first infusion device with TCI [37].

TCI devices allow the anesthesiologist to control anesthesia in an open-loop system bringing safety and accuracy to the procedure. Different TCI devices have been commercialized, such as the Base Primea by Fresenius, figure 1.16 with multiple modules or the Asena PK by Alaris, figure 1.17, which incorporates the Rugloop algorithm.

Figure 1.16: Orchestra Base Primea [3].

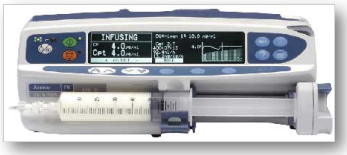

Figure 1.17: Asena PK by Alaris [4].

However, new technologies and concepts as well as the work of researchers brought new devices to be used with TCI and closed-loop control. The OTCI developed by Braun, figure 1.18, incorporates the infusion pump and a monitor with physiological

and haemodynamic data [5].

Figure 1.18: A modular concept for anesthesia - Optimised Target Controlled Infusion [5].

TCI systems have been studied, tested, optimised, analysed and validated over the past 30 years. The ambition of researchers was to take steps to bring automation to anaesthesia. Closed loop control of anesthesia would allow automation of the administration of anesthetic drugs, using monitors and indexes to assess drug effect and TCI systems for drug delivery. Milne described the advantages of a closed-loop control as [38]:

- Adequacy of anesthesia to individual conditions and characteristics and to individual requirements;
- Targets of concentration according to the system feedback either by surgical stimulus or anesthetic procedure;
- Reduction of over and underdosing;
- Less variability of the DOA level.

The complete automation of the procedure could provide the absolute control of drug administration, avoiding overdoses with allowing precise assessment and

maintenance of the subjects physiological functions, decreasing errors and increasing the reliability of general anesthesia [39].

TCI systems are facing improvement, namely with the addition of new tools as neural networks to validate physiological data [40]; Bayesian method integrating TCI technique with physiological data into a mathematical model [41]; genetic data to model and control drug [42] and the closed-loop control as the ultimate frontier [43]. All these contribute to redefine general anesthesia and TIVA.

1.3 A novel contribution to the Improvement of Anesthesia Delivery Systems

This thesis presents the development of an anesthesia SCADA incorporating TCI technique, traditional and novel IRCA, intelligent alarms as an advisory tool for the physician, and acquisition and synchronization data from several devices and monitors. All this in a system suited to work in the operating room environment for clinical purposes. To accomplish this, work was divided into five steps:

1. Driver Communication:

   This task is represented by the implementation of communication drivers for different devices and monitors used in the operating room during general anaesthesia. The implementation of the drivers includes programming the manufactures driver in a common algorithm to all drivers; testing the communication parameters, configuring send received data from the device/monitor and errors log, and validate the final algorithm in a clinical environment.

2. Data Analysis:

Based on the driver communication task, data analysis is composed of three functions: reception, treatment, and recording of data from the devices and monitors. Data received are classified into valid and non-valid, treated for outliers removal and finally placed in the HMI and recorded into secure files.

3. TCI:

   The development of the TCI technique is basically the implementation of two algorithms: the PK/PD model to simulate the drug/behaviour interaction and the IRCA to drive the infusion devices.

   Previous to program the TCI final algorithm, the PK/PD model must be developed as a general algorithm able to receive different anesthetic drugs, such as hypnotics, opioids and muscle relaxants as well as different models. The model algorithm should include routines for special types of patients, namely obese, elderly and infants as well as restrictions associated with the device, such as infusion rate values and special commands.

   The second algorithm programmed is the IRCA and must be preceded by the implementation of a secure communication driver. The communication driver of the infusion device, the actuator of the TCI system, must be implemented, tested and validated until exhaustion before it integrates the IRCA.

4. Intelligent Alarms:

   The intelligent alarms are composed of data collected by the system and clinical conditions pre-set by the physician. The goal is to verify and avoid critical/risk conditions during anesthesia before they occur or are detected by the anesthesiologist.

5. Supervisory Control and Data Acquisition (SCADA):

The final goal is the incorporation of all steps into a singular algorithm, which would be able to:

- Monitor: received data in real time from several devices/monitors;
- Supervisory: treat collected data following pre-defined criteria and specific rules; generate alarms, create an historic and logs to advise the user; record data files and allow the interaction of the user with the process in real time.
- Alarms: advise and/or alert regarding exceptional conditions of the system or the patient.
- Control: automatically apply algorithms to control the infusion device based on the PK/PD simulation. The control is not complete because it requires the full time interaction with the anesthesiologist to judge and decide the next step.
- Record: record all variables collected from the device/monitors in a single file; recording of alarms from devices/monitors; logs from exceptional system alarms, etc.
- Recipes: generate specific clinical protocols or specific sequence of drug administration.
- Historic: a file composed by subject data, physician information, system conditions, clinical protocol followed and any relevant information related to the clinical case.

1.3.1 Thesis Structure

A brief description of the thesis structure is presented in order to guide the reader through the remainder of the thesis and the bulk of the original work developed.

In chapter 1 of this thesis a basic guide for a non physician conceptualizing anaesthesia and anaesthetic drugs is presented. A detailed analysis of development

and implementation of TCI system (hardware and software) in the last 20 years is addressed in this chapter as well as the control strategies such as predict control, fuzzy control and Bayesian-based closed-loop control applied to TCI.

Chapter 2 describes the implementation of 11 different communication drivers into ASYS. The protocol communication for medical devices was approached in detail considering the specific data as: frame structure, data flow, baud rate, parity and algorithms for error detection with inherent parameters for clinical environment. This implementation results in a synchronization software and data base covering 11 devices in the Operating Room (O.R.) displays patient data into a single screen optimizing the physician performance and feedback.

Chapter 3 addresses the implementation of TCI technique and the development of ASYS as a computer-aided for anaesthesia practice. This chapter address the implementation of 5 different PK/PD models: Beth to be used with dogs; Marsh and Schnider for propofol use in adults; Kataria for propofol use in paediatric patients and Minto for the opioid remifentanil. Also in chapter 3 the analytical solution that originates the novel IRCA using Optimal Control is described. The application of the algebraic modelling language (AMPL) and the algorithm of KNITRO solver is introduced to the TCI algorithm. The novel IRCA improves the computational performance of the SCADA, minimizing errors and optimizing the traditional TCI technique.

Chapter 4 introduces the concept of intelligent alarms is introduced as a real-time advisory system to the physician. The physiological variables: heart rate, haemodynamic response, oxygen saturation, carbon-dioxide saturation and the cerebral index (BIS) combined with the drug concentration at plasma or effect-site were set as input to the neural network. The output was represented by intelligent alarms to guide the physician during the anesthesia procedure.

Chapter 5 compiles the results from chapters 2, 3 and 4 about development and the implementation of ASYS to be use in general anesthesia. Chapter 6 presents the main achievements and future works in ASYS.

Chapter 2

Communication Driver

"Computers armed with syringe-pumps do not threaten our existence, but they do provide us with the means to make great strides towards the precise control of drug actions in our patients. C.J. Hull

Introduction

This chapter consists in the study and implementation of the communication protocols of devices and monitors used to develop software for clinical environments. The development of the software to monitor and synchronize data between several different equipments allows a better evaluation and comprehension of the subject under general anesthesia during a surgical procedure.

The communication between hardware and software needs a special algorithm. This algorithm is based on a special translator between user commands and machine language, called driver. The driver is composed by singular rules related with the equipment and by algorithms to secure the data transmitted between the user interface and the device.

This chapter describes the methodology of implementation, the implemented drivers, the communication tests, and the final validation at clinical trial in a veterinary and human O.R..

2.1 Protocol Communication

The communication protocol is composed by the format and the rules of data transmission in or between computing systems. The communication protocol presents the syntax, semantics and synchronization of the communication, as well as internal algorithms for flagging, authentication and error detection of the digital message.

The communication protocols used in the industry or Internet environment could be described as a commercial package composed by a user-friendly customized interface, with options such as security, cryptographic algorithms, authentication, intrusion detection systems, etc. These packages were developed with general instructions for special formats of data and can be customized to be used in several industrial situations with few additional configurations.

However, with the development of biomedical engineering, numerous equipment and communication processes are still in development and validation phase to be approved and used in clinical environments. The communication protocol used by these computing systems requires special rules and procedures, intimately related with the medical procedures and clinical environments, which were never addressed before. Before detailing the communication protocol of each equipment implemented in ASYS, an overview about communication protocols, from the network set-up to the security algorithms used by protocols, will be presented.

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2.1.2 Communication Channel

The way the communication is maintained characterizes the connection; the language used to communicate characterizes the rules to establish the communication.

The maximum communication rate is proportional to the transmission power and is inversely proportional to the noise. The best performance expected from a communication system is transmitting data with low power and without noise.

The communication systems are composed by: protocol, code and message. The protocol describes the data format, the code specifies the symbols used to transmit the data and the message is the information or digital data.

Data can be transmitted and maintained under two forms: wired or wireless [44].

- Wired:

  The signal is propagated within a physical limit; in other words, the signal is guided through a specific path (cable or wire). The signal transmitted this way is subject to noise and interference. The interference can be avoided with the physical capabilities of the cable and its application. The average velocity of data transmission is superior to wireless form.

- Wireless:

  The signal is propagated through the air without physical limits. The propagation is based on electromagnetic sources, such as radio, infrared, etc. This connection can provide mobility when compared to the wired connection. However, the signal transmitted this way is also subject to noise and interference, been difficult to be avoid.

2.1.3 Data Flow

After the channel for data transmission between systems is defined, it is important to set the data transmission mode as:

1. SIMPLEX: communication is maintained between sender and receiver. The data travels from sender to receiver; the opposite direction is absent.

2. HALF-DUPLEX: this is similar to duplex communication; however, the receiver waits to receive data from the sender to send a receipt confirmation message.

3. FULL-DUPLEX: communication is maintained between sender and receiver with data flow in both directions. Each end of the frame can thus transmit and receive at the same time, which means that the bandwidth is divided in two for each direction of data transmission if the same transmission medium is used for both directions of transmission.

2.1.4 Units of Measure for Data Communication

The smallest measurement unit for data is called BInary digiT (BIT), which is also defined as the smallest unit of data storage. One BIT can represent two vales "0" or "1", true or false, low or high level, depending on where the data came from.

The combination of 8 bits composes a Byte. Considering one byte is composed by 8 bits, 1 byte can represent 256 binary numbers. Therefore, 1 byte can represent letters, punctuation, accentuation, numbers, special characters, etc.[45]

Aiming to improve the translation of 0's and 1's, a standard code for system communication was developed. The scheme codification relates binary numbers with symbols composing the American Standard Code for Information Interchange (ASCII) code. The ASCII code is used in communication in and between computing systems, communication equipment and any device that uses text to transmit data.

Frame: represents the digital data transmission unit or a data packet on the Layer 2 of the OSI model [46].

2.1.5 Data Transmission

Data transmission is defined as the data transfer between two or more computing systems. The relevant issue to consider in the communication between two equipments is the type of signal used to transmit the data. Therefore, the transmitted signal could be continuous or discrete [47].

Continuous Signal: a mathematical function of an independent variable $t \in \Re$, where $\Re$ represents a set of real numbers. It is required that signals are uniquely defined in t except for a finite number of points, as shown in figure 2.1:

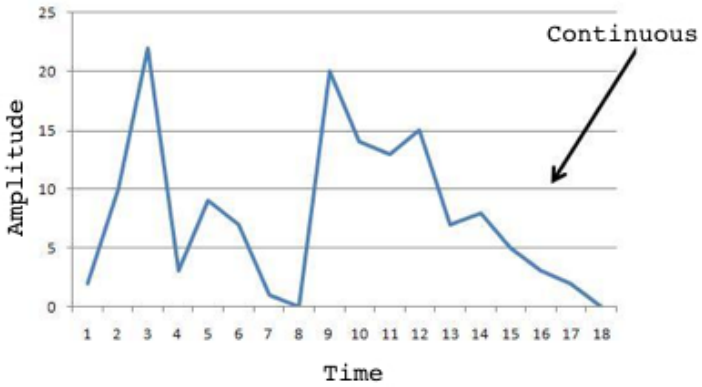

Figure 2.1: Continuous signal

A discrete signal is a uniquely defined mathematical function (single-valued function) of an independent variable $k \in Z$, where Z denotes a set of integers, as shown

in figure 2.2:

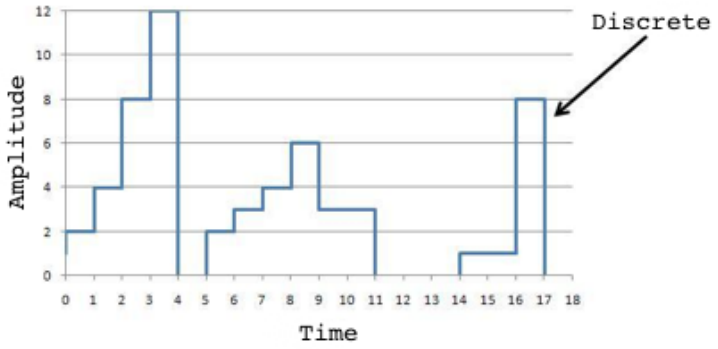

Figure 2.2: Discrete signal

Digital Signal: this signal is composed by finite states, discrete in time and amplitude.

Analogue Signal: this signal is composed by infinite states (non-measurable and non-discrete) of values.

2.1.6 Confined Transmission

The confined transmission of data can be described by two types:

1. Parallel: this type sends N bits simultaneously through a physical support, such as a cable.

2. Serial: this type of transmission send one bit at a time sequentially over a communication channel.

The serial transmission can be classified by the synchronization of control characters.

Types of Series Transmission

Synchronous Transmission: A clock synchronizes the data transmission between sender and receiver.

The receiver knows the time delay between the data and can identify the bit sequence and the interval from T to T seconds. This interval represents the data transmission speed ($1/T$) related to the clock. This type of transmission does not need control bits, enabling the transmission of large data frames.

Asynchronous Transmission: there is no clock between sender and receiver. The data exchange is synchronized by control bits inserted in the beginning and end of the data frame.

When the sender sends a byte to the receiver, it starts with a bit called start bit, flagging the start of the data frame transmission. After the data frame is sent, it is possible to send a bit, called parity bit, to verify all data was correctly transmitted.

In the end of the transmission, 1 or 2 bits called stop bits are sent to conclude the transmission between the systems [48].

Parameters of Asynchronous Transmission

Considering that asynchronous transmission is defined as serial communication with one physical transmission support, the communication between sender and receiver must be configured before the communication starts.

The basic data transmission configuration is defined by: speed (bits/s), start bit, parity bit and stop bit described as follow:

- Transmission Speed: number of bits transferred per second, including the start bit, data bit, parity bit and stop bit. A common value of baud rate is 9600 bits/sec, meaning the communication port sends the data frame at 9600 bits each second.

- Start Bit: the first bit sent before the data frame. When the channel is idle the logic level is '1', or ON. During the data transmission between the sender and the receiver, the start bit is '0', or OFF, flagging the beginning of communication.

- Stop Bit: the last bit used to indicate end of transmission. When the transmission ends, the stop bit logic level is '1', flagging the idle channel.

- Parity Bit: the function of this bit is detecting errors during data transmission. The parity can be even, odd, mark or space. The mark and space are not commonly used. The detection process is described as follows: In the frame "00101110" with even parity, the parity bit parity is set at 0, resulting in an even number of 1's. In the frame "00101110" with odd parity, the parity bit is set at 1, resulting in an odd number of 1's.

When the transmission ends, the computing system tests the parity and the sent frame, and, if necessary, a message is sent to log the errors occurred during communication. Figure 2.3 shows the structure of the data frame:

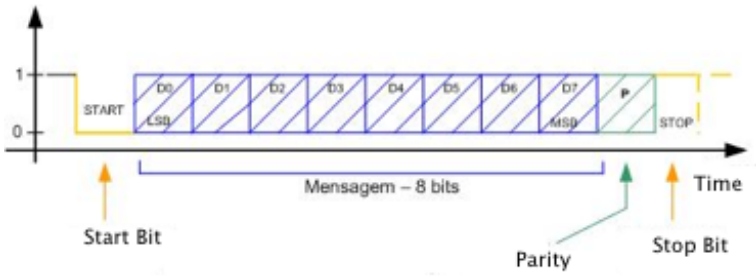

Figure 2.3: Frame of a transmission asynchronized

2.1.7 Error Detection

BER: Bit Error Rate is the probability of error of one bit during a period of time.

$$Perroframe = \sum_{k=1}^{n} \binom{n}{k} (1-p)^{n-4} = 1\,(1-p)^{n} \tag{2.1}$$

Where: P : probability of corrupted bit = BER 1-p = probability of bit not corrupted n = number of bits in the frame

The frame error (Perrorframe), equation 2.1, is the number of incorrectly transferred data frames. A frame is assumed to be incorrect if at least one of its bit is incorrect [44].

The confined or not confined transmission is suitable to a bigger or smaller level of interference, noise, signal attenuation or signal distortion problems related with the environment where the signal is transmitted. The environment, the material of the cable through which the signal is transmitted, the distance between sender and receiver, the channel connection, the power sources and the networks are some of the interference factors in data transmission.

The physical improvement of these factors and conditions does not either guarantee a correct data transmission, or avoid the wrong transmission of data bits. The interference is the cause of errors during data transmission. To minimize data transmission errors, corrupted or lost data, algorithms to detect and correct errors have been developed.

The detector algorithm assembles into the frame, information for the receptor. This information represents error to the receptor which will require the retransmission. The correction algorithm assembles information into the frame to highlight the correction in the data. The detection codes can be: parity detection, checksum, and cyclic redundancy check (CRC) [49].

Parity Bit: when present in the frame, the parity bit checks for errors in the byte. It is used in serial communication.

Checksum: generic denomination for cycle verification. It's commonly used in low level communication and automatically in series protocol communication. A verification pack is added to the frame to check for errors. The checksum can be calculated, for example, by addition. After receiving the frame the receptor checks if the sum of characters corresponds to the send and verifying the correct transmitted frame. This type of detection does not allow identifying reorganized bytes in the frame, the insertion or removal of bytes with '0', or errors that do not change the checksum result.

This method is not consider very robust when used alone, that's why it's commonly combined with other techniques like CRC.

CRC: in the cyclic redundancy check the frame is check by the mathematical division, while in the checksum is the addition.

CRC - Cycle Redundancy Check

The CRC presents an 99.9985% index of error detection [50]. The CRC function divides the bits of a frame by a set of bits and uses the operation remainder as a checksum. In the CRC algorithm, the bits from the frame are considered a polynomial with 0 and 1 coefficients. In the algorithm, the set of bits is a collection of coefficients from a polynomial with k terms of k-1 order. Considering the message 10110101 [50]:

$$1 \cdot x^7 + 0 \cdot x^6 + 1 \cdot x^5 + 1 \cdot x^4 + 0 \cdot x^3 + 1 \cdot x^2 + 0 \cdot x^1 + 1 \cdot x^0 \tag{2.2}$$

The arithmetic manipulation used in a CRC algorithm is done in base of 2 following the algebraic theory. In the addition operation there is not transference and in the subtraction there is not the method of borrowing. Therefore the multiplication is executed normally and the division following the binary code.

The CRC algorithm considers the frame message to be transmitted as a binary word M. M is divided by G, a specific word, known by both the sender and the receiver. The remainder of this division, R, is the checksum[50].

Theory of Polynomial Code

$$\frac{M(x) \cdot 2^n}{G(x)} = Q(x) + \frac{R(x)}{G(x)} \tag{2.3}$$

$$[M(x) \cdot 2^n] + \frac{R(x)}{G(x)} = Q(x) \tag{2.4}$$

$$[M(x) \cdot 2^n] + \frac{R(x)}{G(x)} = Q(x) + \frac{R(x)}{G(x)} + \frac{R(x)}{G(x)} \tag{2.5}$$

Considering the example, the CRC algorithm can be described as follows:

The message to be transmitted: $M(x) = 10110101$ is converted into polynomial with k terms k-1 order;

$$1 \cdot x^7 + 0 \cdot x^6 + 1 \cdot x^5 + 1 \cdot x^4 + 0 \cdot x^3 + 1 \cdot x^2 + 0 \cdot x^1 + 1 \cdot x^0 \tag{2.6}$$

$$M(x) = x^7 + x^5 + x^4 + x^2 + 1 \tag{2.7}$$

The polynomial generator is known by sender and receiver, for example, $G(x) = 10011$:

$$G(x) = 1 \cdot x^4 + 0 \cdot x^3 + 0 \cdot x^2 + 1 \cdot x^1 + 1 \cdot x^0 \tag{2.8}$$

To the polynomial generator order is added W zeros to the message M(x);

$$M(x) + W = 101101010000 \tag{2.9}$$

The division in base of 2 of M(x) + W for G(x);

$$M(x) + W = M(x) \tag{2.10}$$

$$\frac{M(x) \cdot 2^n}{G(x)} \tag{2.11}$$

The remainder is known $R(x)$ and the message is transmitted. The receiver divides the message received by the polynomial generator. If the remainder of the division is zero the message has no errors. If the reminder is different than zero the message has errors and must be retransmitted.

The message transmitted is a multiple polynomial of the generator G. When the message is corrupted during the transmission, the receiver term is $M(x) + E(x)$, where E(x) is an error vector. Receiving M(x) or $M(x) + E(x)$ the receiver divides the message by G.

$$\frac{M(x) + E(x)}{G(x)} \tag{2.12}$$

Considering $M(x)/G(x)$ is equal to zero, the division of $E(x)/G(x)$ presents the error detected. The generator polynomial must guarantee the detection of all types of errors. If E(x) is a multiple of G(x) some errors can not be detected. Considering this issue, the polynomial generator must be from a class of G(x), where small interferences can be detected.

The most common polynomial generators are:

$$CRC - 16 = x^{16} + x^{15} + x^2 + 1 CRC - CCITT = x^{16} + x^{12} + x^5 + 1 CRC - 32 = x^{32} + x^{26} + x^2$$

The 16 and 32 represents the message bits, therefore CRC-16 can be identified by: 1 1000 0000 0000 0101.

2.1.8 Standard Serial Transmission RS - 232C

Standard EIA (Electronic Industries Association - USA) RS: Recommended Standard. 232: norm number. C: norm revision.

Serial asynchronized communication, can be maintain confined or not confined.

Interface characteristics:

- Baud rate: from 75, 115.200 bits/sec or more;
- Connection between computing systems: less than 15m without amplification, up to 1200m with amplification;
- No electrical isolation between equipments.

Signal electrical characteristics:

- Power level: -25V to -3V for logic level '1', +3V up to +25V logic level '0';
- Function: OFF '1', ON '0';
- Signal: mark to represent '1', space to represent '0'.

Data Format - Serial Communication

The standard of data format of the designation 8-E-2 means: 8 data bits, parity even, 2 stop bits. [44]

For this type of transmission the data communication is exemplified by figure 2.4:

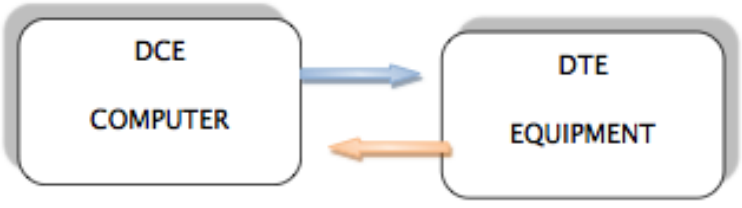

Figure 2.4: Data Terminal Equipment: Computer, Data Circuit Terminating Equipment:Equipment

Data Terminal Equipment (DTE): data source equipment; Data Circuit - Terminating Equipment (DCE): equipment with functions to keep the connection and convert the signal in data.

The connection between DTE and DCE is maintained at confined way with a cable described by the RS232 standard. The standard specifies a connection with a 25-pin connector; however the most common connector used in this communication has 9 pins.

To establish the communication between DTE and DCE, 3 pins are needed: one to send data, one to receive data and one to be the reference for analogue signals. The following table describes the pins and the signals 2.5:

PIN	DESIGNATION	SIGNAL	TYPE
1	CD	Carrier Detect Control	CONTROL
2	RD	Received Data	DATA
3	TD	Transmitted Data	DATA
4	DTR	Data Terminal Ready	CONTROL
5	GND	Signal Ground	GROUND
6	DSR	Data Set Ready	CONTROL
7	RTS	Request to Send	CONTROL
8	CTS	Clear to Send	CONTROL
9	RI	Ring Indicator	CONTROL

Figure 2.5: 9 pin connector - RS232.

The message is transmitted by the TD (Transmitted) pin, the RD (Received Data) pin receives the data and the GND (Ground) pin is the reference signal. Considering half-duplex or simplex communication, the pins to transmit data are TD and GND, the message is transmitted from DTE to DCE. Full-duplex communication uses pins TD and RD to transmit data from DTE to DCE, as shown in figure 2.6:

The control pins RTS, CTS, DTR, DSR, CD and RI manage the data transmission. The RTS and CTS pins indicate when the equipment is ready to receive and transmit data.

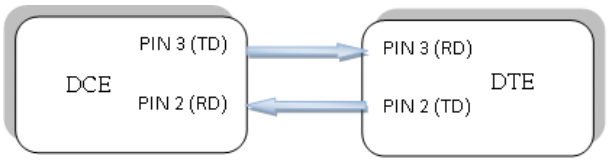

Figure 2.6: Connection between DTE and DCE with transmission from TD and reception from RD.

Request to Send (RTS): pin used by Data Terminal Equipment (DTE) to sign to Data Circuit - Terminating Equipment (DTE) the data transmission; Clear to Send (CTS): pin used by Data Circuit - Terminating Equipment (DCE) to sign to Data Terminal Equipment (DTE) ready to receive data;

The DTR and DSR pins indicate equipment On and ready to transmit data; Data Set Ready (DTR): pin used by DTE to request connection in the DCE; Data Terminal Ready (DSR): pin used by DCE to indicate power ON and connect.

The CD and RI pins indicate a specific modem-modem connection. CD (Carrier Detect): pin used by the modem to indicate a connection with another modem; RI (Ring Indicator): path is pin indicates sign ready; A cable with a DB9 connector is used to establish the connection between DTE and DCE. The 9 pin configuration is described in figure 2.7:

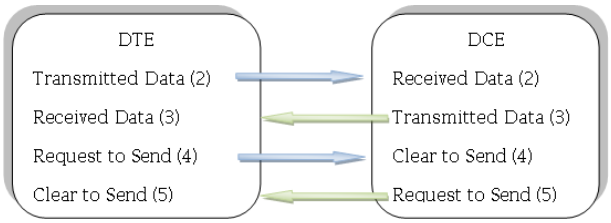

Figure 2.7: Connection between DTE and DCE with transmission from TD and reception from RD.

Several connections were describe by the literature to connect two DTE [44].

The connection Null Modem is the most used. This connection mimics the connection between a DTE and a modem where the pins DTR, DSR, CD were jump without connection with the other DTE. The pins RTS and CTS are also jumped, therefore the two DTE presents signal for connect and start communication. The pins

RD, TD e GND are normally connected, as shown in figure 2.8, to maintain data transmission.

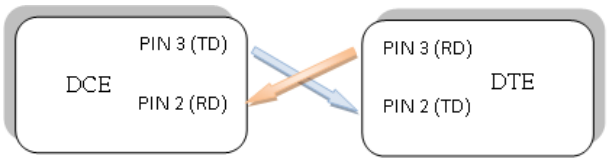

Figure 2.8: Serial Cross Connection.

The flow control between DTE and DCE can be done by hardware RTS/CTS or by software XON/XOFF. The XON/XOFF control uses ASCII characters, XON is represented by 17 and XOFF is represented by 19. When the DCE buffer is full, the signal transmitted is the character 17; when the buffer is empty, the character transmitted is 19. The RTS/CTS control uses two additional connections in serial communication. When the DTE sends a message, it activates the RTS. When the DCE is ready to receive the message, it activates the CTS and starts the transmission.

2.2 Communication Drivers

2.2.1 Neurophysiological Monitors

The anesthesia procedure can be considered successful when the quantity of drug titrated to the patient results in the expected anesthetic condition allowing the surgical procedure with comfort and security to the patient. However, the amount of drug administered to the patient is sometimes less than expected, causing awareness. The awareness episode is an explicit recall of events, surgical or not, during anesthesia by the patient [51]. The risk of awareness increases with the use of muscle relaxants that allow the surgeon activity but preclude the conscious patient response during an intra-operative recall. If the muscle relaxants do not produce analgesia or hypnosis, once paralyzed and conscious the patient will be aware of the surgical procedure, with traumatizing consequences.

The development of cerebral activity monitors aims to alert the physician to a decrease in the level of anesthesia or possible awareness episodes. These monitors are mainly based in the EEG. The measure of the electrical signal from the cortex is direct related with opioid and hypnotic drugs changing the amplitude and frequency of the signal.

Bispectral Index

The bispectral index is an EEG based parameter that correlates very well with the concentration of hypnotic drugs, allowing objective assessment of the level or adequacy of anesthesia. The index results from the application of a proprietary algorithm. The level of burst suppression of the EEG and EMG activity are known to be taken into account for the calculation of the bispectral index.

This DOA monitor, besides the bispectral index, also provides total power analysis and time domain analysis. The combination of these techniques optimized the analysis of EEG and the clinical effects of anesthesia [6].

To measure the cerebral activity a four electrodes sensor is placed on the forehead, as shown in figure 2.9. The signals captured by the sensor are transmitted to a digital converter (DSC), 2.10. The signal sent to the monitor is processed, resulting in a DOA index.

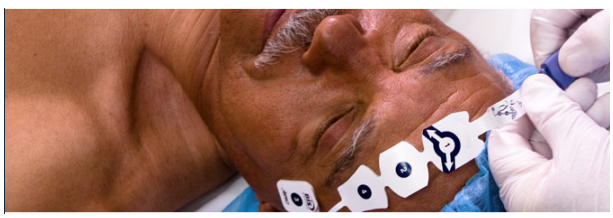

Figure 2.9: Standard positioning of BIS sensor - model Quatro [6].

The Bispectral Index (BIS) represents a tool that allows the physician to evaluate mainly the hypnotic component of general anesthesia. BIS uses a scale from 0 to 100, where 0 represents the isoelectric signal (very deep anesthesia or coma) and

Figure 2.10: Digital Signal Converter - BIS [6].

100 represents full arousal (awake subject).

The BIS monitor became a very useful tool in anesthesia practice around the world, optimizing subject monitoring and proving to be a powerful indicator of DOA.

The synchronization of this monitor, figure 2.11 with a computing system is valuable as data acquisition considering the relevance of the monitor during anesthesia and the possibility of correlation between drugs concentration and DOA [6].

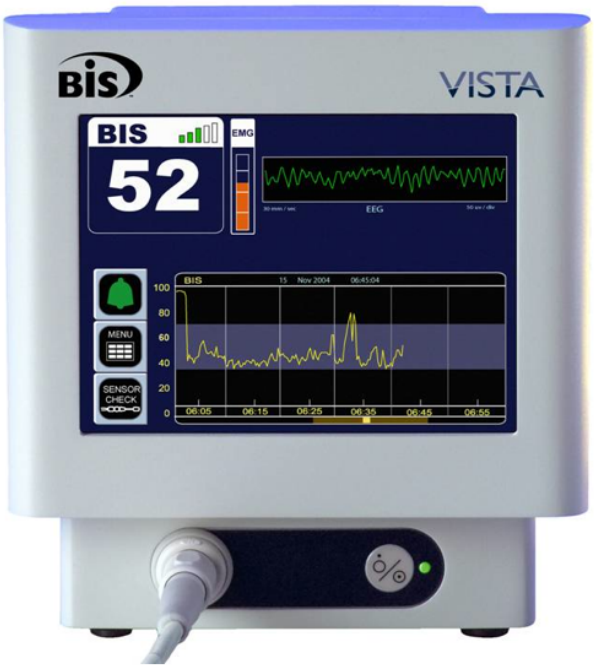

Figure 2.11: Monitor BIS model Vista [6].

The BIS monitor has one RS232 communication port located in the bottom part of the monitor. The communication protocol is asynchronous serial communi-

cation; the frame can be specified in ASCII or Binary code according to user preset [6].

The connector used in the communication is female DB9. The monitor becomes DCE equipment and the connection follows the configuration presented in figure 2.12:

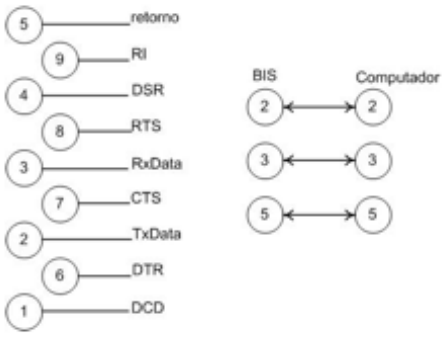

Figure 2.12: Female DB9 Monitor BIS.

The parameters of the communication are:

- Baud rate: 9600 (ASCII), 57600 (Binary)
- Data bits: 8
- Stop bit: 1
- Flow Control: not recommend

The data frame sample time is 5s, the data in the frame is: the BIS index, SQI signal quality, burst suppression SR, spectral frequency SEF, EEG and Total Power (TOTPOW).

The implementation of the communication protocol started with a simple test of communication between the monitor and a computing system with the Microsoft Hyper Terminal software. After establishing communication and recognizing the data and the frame pattern, the communication algorithm was developed in the LabView (National Instruments) programming language. BIS sends data through the serial port

every 5s without any requirement from the computer.

The LabView programming language is a structured language, as shown in figure 2.13. The left block, in figure 2.13, represents the logic to "open" the communication channel between BIS and the computing system. The parameters of the communication were inserted in the block to define the specific communication protocol. The right block, in figure 2.13, represents a "while" loop where the equipment communication port is read every 5s or 5000ms or until the user stops the communication.

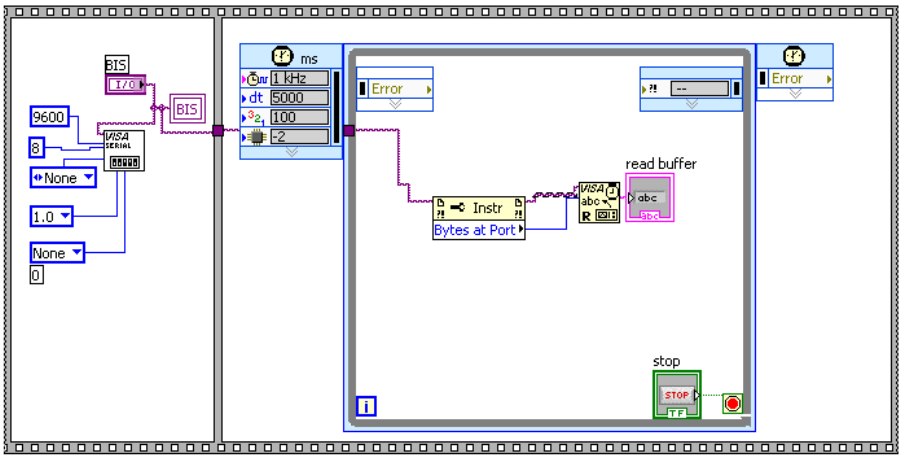

Figure 2.13: Monitor BIS Communication Routine.

The data collected from the frame is captured and processed by a second algorithm presented in figure 2.14; the right block shows how the data from the frame is selected and processed.

A relevant part in programming drivers is building a friendly user interface. The BIS user interface is presented in figure 2.15, with the relevant information and variables captured from the frame, the data is refreshed at sample time of 5s by the monitor.

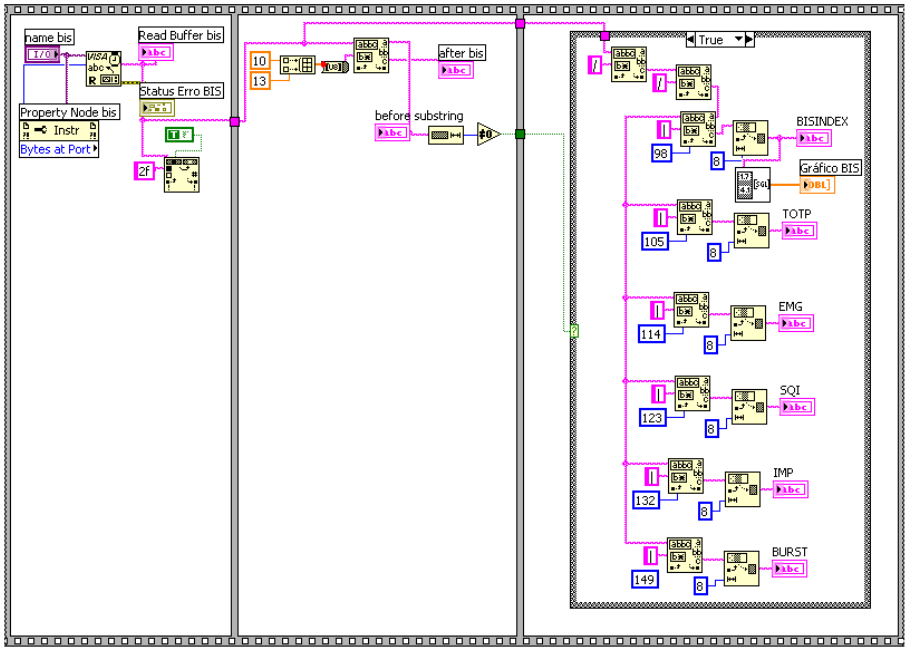

Figure 2.14: Monitor BIS Data Process Routine.

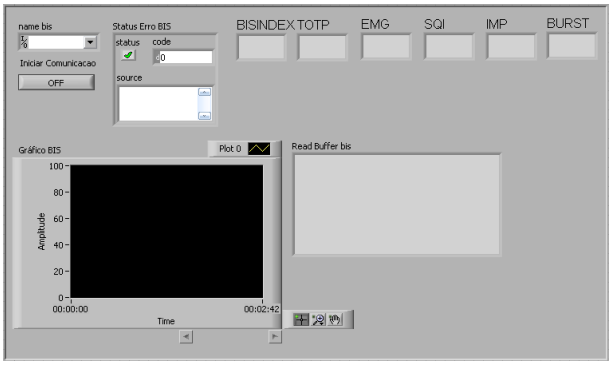

Figure 2.15: Monitor BIS - Develope User Interface Test.

Auditory Evoked Potentials

The technology of auditory evoked potentials uses auditory stimuli applied to the ears and measures the electrical response to these stimuli that occurs in the brain. Headphones are placed on the subjects ears to deliver the auditory stimuli and three skin electrodes are applied to the head to pick up the electrical activity, as shown in figure 2.16:

EEG averaging is the technique used to separate EEG random activity from the evoked potential. The mid-latency portion of the potential, namely its latency and

Figure 2.16: Positioning of headset and electrode of AEP [7].

amplitude, are used to calculate the ARS AEP index. The AEP index goes from 0 to 100, with 0 representing an absent potential and 100 representing maximum activity. The range for adequate surgical anesthesia is from 15 to 25. The index allows identifying the DOA during general anesthesia [7].

The choice of a DOA monitor is related with skill, individual experience and confidence of the physician to use the monitor as well as in scientific evidence. The inclusion of the AEP Monitor/2 in ASYS resulted from the fact that it was being used clinically as an alternative to BIS or in conjunction with BIS for research purposes.

The communication between AEP and the computing system is RS232(C) asynchronous serial communication with binary data format. The communication port is located at front of the monitor, as shown in figure 2.17 [7]:

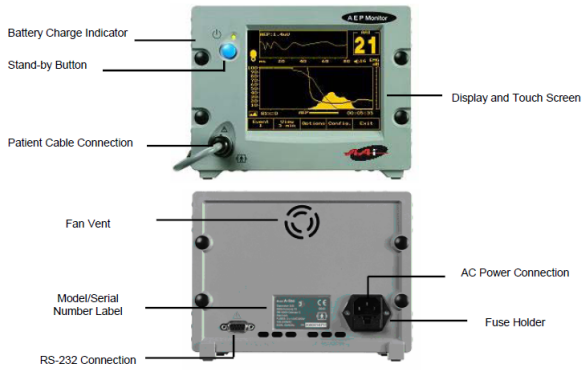

Figure 2.17: AEP Monitor/2 by Danmeter [7].

The monitor presents DCE characteristics during the communication and the connector used for communication is a DB9 male. The parameters of serial communication for this monitor:

- Baud rate: 9600 or 115200
- Data bits: 8
- Stop bit: 1
- Parity: none
- Flow Control: none

The serial communication protocol maintains the data transfer between the monitor and the computing system. The data in the frame are: monitor version, date/time, index AAI, impedance, event counter, noise index, burst suppression, EMG [dB]. The data capture is maintained by a single channel.

The implementation of the AEP communication protocol started with a simple communication between the monitor and a computing system with Microsoft Hyper Terminal. After establishing communication and recognizing the data frame pattern, a specific algorithm was developed using LabVIEW by National Instruments.

The routine to open the communication port was similar to the one described before for the BIS monitor, as demonstrated in figure 2.18, the left block represents the logic to "open" the communication channel; the right block, in figure 2.18, represents a "while" loop where the equipment communication port is read every 5s or 5000ms or until the user stops the communication:

The left block represents the algorithm to open the communication port and maintain the communication active during data capture. The right block represents the algorithm to receive and process captured data.

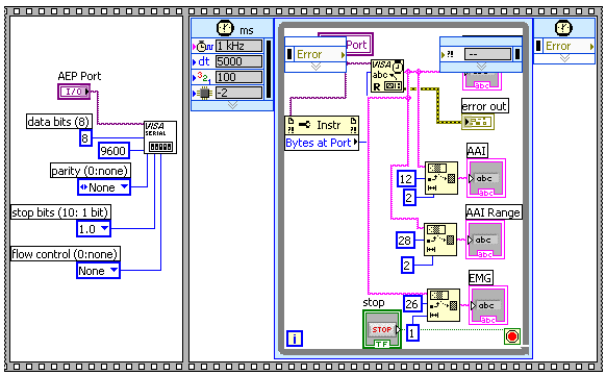

Figure 2.18: AEP Monitor/2 communication routine.

2.2.2 Physiological Monitor

Anesthesia Modular Monitor - DATEX Ohmeda S/5 - General Electrics (GE)

Monitoring of physiological variables during the anesthetic procedure is essential; not only because it allows the assessment of the patients status but also because it helps titrate anesthetic drugs.

This monitor incorporates modules for different parameters, namely for the assessment of oxygenation, ventilation, hemodynamics (arterial and venous pressures, heart rate, pletismography, etc), temperature, neuro-muscular block, cerebral activity and several others. These monitors also allow data storage and retrieval.

The vital signs monitor incorporated in ASYS was the DATEX Ohmeda S/5 marketed by GE, as shown in figure 2.19. The oxygenation and hemodynamic variables are relevant variables to be monitored before anesthesia induction and, during the entire surgical procedure.

The synchronization and centralization of all data from the vital signs monitor and the cerebral monitor makes it easier for the physician to analyze the compiled data and make decisions during the procedure. This information tool improves the efficiency of the physician, decreasing time spent in the evaluation of the information

Figure 2.19: Datex Ohmeda S/5 in the O.R. [8].

coming from several different monitors.

This monitor has different modules to capture data. The communication between monitor and the computing system access and synchronized the data capture by the modules, as figure 2.20. The data captured from this monitor can be transferred by memory card, network or RS232 serial communication.

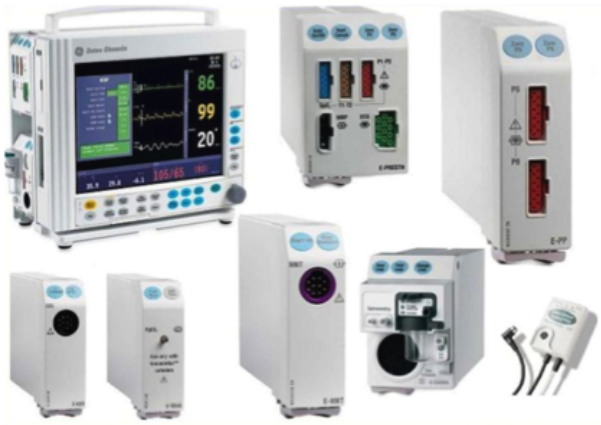

Figure 2.20: Datex Ohmeda S/5 and modules GE.

The data transmission is maintained by the communication port in the back of the DATEX. The communication protocol is RS232 asynchronous serial. The connector used is male DB9, following the configuration in figure2.21:

Parameters of serial communication for this monitor:

- Baud rate: 19200 bit/s
- Data bits: 8

PIN	Signal
2	RxData
3	TxData
5	GND
7	RTS
8	CTS

Figure 2.21: Datex Ohmeda S/5 - DB9 configuration.

- Stop bit: 1
- Parity: even
- Flow Control: CTS/RTS

The implementation of the DATEX communication protocol started with a simple communication between the monitor and a computing system with Microsoft Hyper Terminal, following indications from the user guide [8]. After establishing the communication and recognizing the data frame pattern, a specific algorithm was developed using LabVIEW by National Instruments.

The communication protocol of the DATEX monitor follows a protocol model called High Level Data Link Control (HDLC). The HDLC is a data link layer protocol published by ISO [52]. It is a variation of the Synchronous Data Link Control by IBM, a protocol in which the receiver examines individual bits looking for control information during the data transmission. The structure of the frame of the HDLC protocol is represented in figure 2.22:

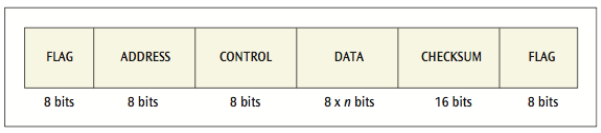

Figure 2.22: Frame structure of HDLC.

The difference between HDLC and SDLC is basically the size of the components of the frame, where HDLC presents addresses with more than 8 bits and a checksum with 16 or 32 bits.

This high level data link control has specific rules to transfer data and guarantee the physiological data is not corrupted or generates errors, as follows:

- Specific Character: the DATEX monitor uses the ASCII character 0x7E to flag the beginning and the end of the frame
- Key: to start the frame transfer, a key must be send. This "key" is compose by: the length of the total data frame, counter, monitor version, date/time. The key must be compliant with the ASCII code little-endian format.
- Format and Order: the data frame is in Intel format, the little-endian format.

The little-endian format places the less significant byte from the data in the lower address (position) of the frame and, consequently, the most significant byte in the upper address of the frame. The communication frames are usually transferred using the big-endian format, which places the less significant byte from the data in the upper address and the most significant byte in the lower position, as shown in figure 2.23:

Figure 2.23: Intel Format of data frame format.

The following tables 2.24, show the Big-Endian order and format and the Little-Endian order and format.

Data transmitted from DATEX uses the little-endian format. The data size is considered as: char corresponds to 1 byte, short corresponds to 1 word or 16 bits and long corresponds to 2 words or 32 bits. The data frame is organized according to the data captured from the modules.

The data size is related with its origin module being char, short or long; the data from a specific module contains a heading with the related physiological name.

Big Endian Format

Address	Order
1600	1001 1010
1599	0010 0110

Little Endian Format

Address	Order
1600	0010 0110
1599	1001 1010

Figure 2.24: Big Endian and Little Endian Formats.

Each module has a data size in the final data frame transfer. The data from each module is presented in ASCII code plus a checksum to validate the data transfer. The frame size is not constant depending on the modules connected to the DATEX in the moment of capture.

The communication algorithm follows the specific rules of the HDLC, as shown in figure 2.25.

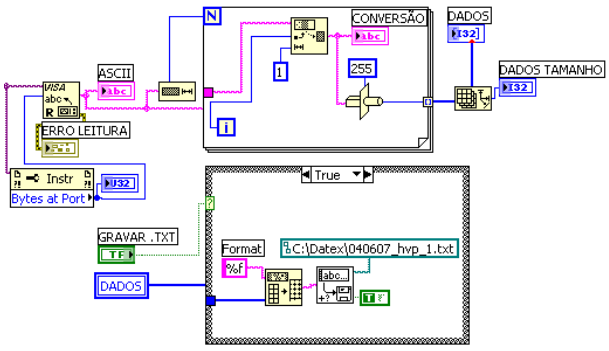

Figure 2.25: Communication algorithm for DATEX.

The data received from the DATEX monitor is treated by a LabView algorithm to be displayed in the interface and synchronized with all data in the O.R.. The algorithm is not totally presented here, considering the 200-variable logic.

INVOS Oximeter Somanetics

The assessment of cerebral oxygenation is indicated is selected procedures, namely when there is a risk of cerebral ischemia. This can be done non-invasively through the use of a dedicated specific monitor and electrodes applied to the forehead. The INVOS is one of such monitors; it uses NIRS technology or Near Infra Red Spectroscopy, with a light emissor and two light receptors applied to each side of the forehead; measurement of regional brain oxygen saturation is obtained. Relative changes in oxygen saturation are clinically very useful.

Cerebral oxymetry is quite useful for the overall assessment of the cerebral effects of anesthetics. Anesthetic drugs reduce brain metabolism and reduce EEG activity and the BIS; however, electrical activity or the BIS may also be result from brain ischemia. In doubtful situations, the presence of adequate cerebral oxygenation will exclude ischemia as the cause of reduced electrical activity. Adequacy of cerebral oxygenation is also related to hemodynamic variables (arterial pressure, heart rate, cardiac output), so it makes all the sense to incorporate all these variables in ASYS. The INVOS (In Vivo Optical Spectroscopy) brain oximeter is shown in figure 2.26:

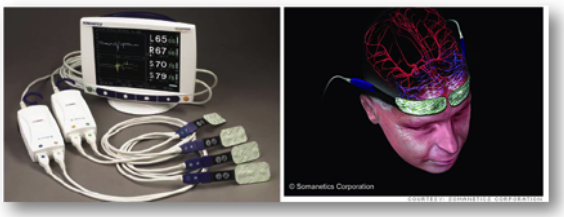

Figure 2.26: In Vivo Optical Spectroscopy - INVOS [9].

INVOS uses an RS232 communication port to transmit data. The communication protocol is asynchronous serial communication, and the data frame is sampled in ASCII code every 5s by the monitor, without any requirement from the computer.

Parameters of serial communication for this monitor:

- Baud rate: 9600 bit/s

- Data bits: 8
- Stop bit: 1
- Parity: none
- Flow Control: hardware.

The connector configuration is null modem. The algorithm for data transmission is similar to the algorithm for the BIS monitor. Figure 2.27 presents the routine with the port communication at left side, and in the block at right side, the read buffer to receive data from the monitor.

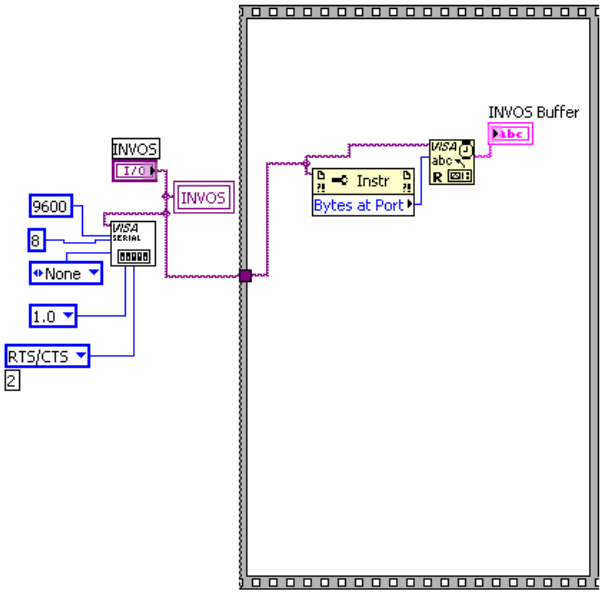

Figure 2.27: Communication algorithm for INVOS monitor.

Another part of the algorithm, figure 2.28 receives the frame, figure 2.29, from the monitor and processes the data by synchronizing it with other variables in ASYS, the structure showed in figure 2.28 represents the filter that processes the data from the frame [9].

LIDCOrapid LIDCO Group Plc

Hemodynamics and pharmacokinetics of anesthetic drugs are closely related [53],[54].

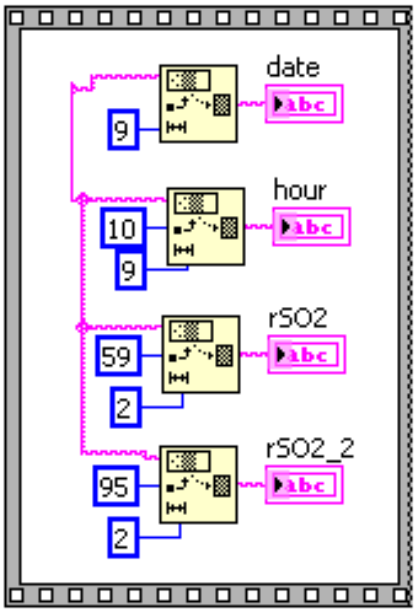

Figure 2.28: Data synchronize algorithm for INVOS monitor.

COLUMN	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
DESCRIPTION	Date	Time	rSO_2	Event Mark	Status	A	B	C	D	rSO_2	Event Mark	Status	A	B	C	D

COLUMN (continued)	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD
DESCRIPTION(continued)	rSO_2	Event Mark	Status	A	B	C	D	rSO_2	Event Mark	Status	A	B	C	D

COLUMN (continued)	AE	AF	AG	AH
DESCRIPTION (continued)	Channel 1 Sensor I.D.	Channel 2 Sensor I.D.	Channel 3 Sensor I.D.	Channel 4 Sensor I.D.

Figure 2.29: Data frame structure of the INVOS monitor.

Cardiac output is probably the variable that provides more information for the assessment of the hemodynamic status of the patient. Until recently it could be measured only by highly invasive techniques. Currently, minimally invasive monitor like the LIDCO, allow a much easier access to cardiac output. The LIDCOrapid monitor, shown in figure 2.30, measures cardiac output continuously through information aquired from the continuous arterial pressure tracings obtained by the Datex vital signs monitor. The LIDCOrapid calculates the systolic volume (SV) and, based on the heart frequency, the monitor samples the variables displayed in the monitor as: arterial pressure, cardiac output and systolic volume.

An arterial catheter inserted during the induction of anesthesia enables the measurement of arterial pressure. Based on the measured arterial pressure, the LIDCOrapid calculates the systolic volume (SV) and, based on the heart frequency, the

Figure 2.30: LIDCOrapid Cardiac Output measurement [10].

monitor samples the variables displayed in the monitor as: arterial pressure, cardiac output and systolic volume.

The monitor uses an RS232 port for communication. The communication protocol is asynchronous serial communication, and the data frame is sampled in ASCII code every 5s. The data frame contains a CRC for detection of communication errors.

Parameters of serial communication for this monitor:

- Baud rate: 57600 bit/s
- Data bits: 8
- Stop bit: 1
- Parity: none
- Flow Control: none.

The connector used to transfer data is a female DB9 termination, RS232 standard configuration. The data frame provides carbon monoxide (CO), heart rate (HR) and arterial pressure.

The algorithm to synchronize and process the data frame is partially presented in figure 2.31:

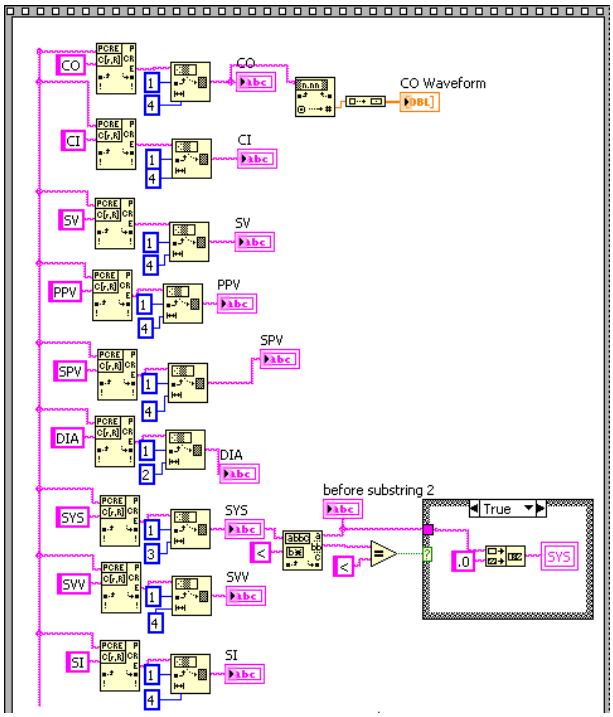

Figure 2.31: Data capture algorithm for LIDCOrapid Cardiac Output.

2.2.3 Actuators

Infusion Pumps

The first studies with microprocessors were by Schwilden [21]. The concept of TIVA was optimized, bringing safety and accuracy to the anesthetic procedure and economic advantages in drug administration.

Two communication protocols were developed in this study; one communication protocol to remotely control the infusion pump and another to acquire data from an infusion pump with an encapsulated TCI system.

The communication protocols of ASENA GH / MK III, figure 2.32, and ASENA PK, figure 2.33, are very similar, with only a few different commands. Both

equipments have a communication port in the back panel. The communication between the infusion pump and the computing system is maintained by the serial or infrared ports located in the back panel.

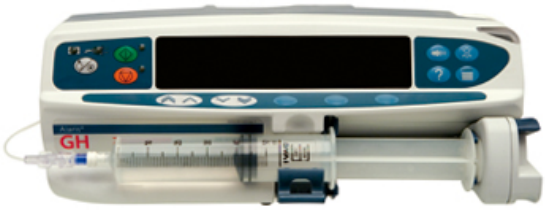

Figure 2.32: Infusion pump by Alaris model Asena GH MK III [4].

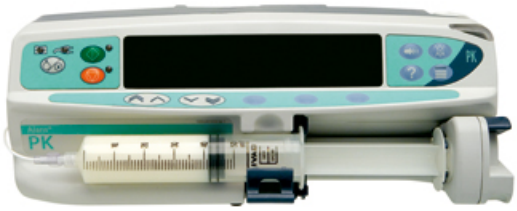

Figure 2.33: Infusion pump by Alaris model Asena PK [4].

The communication protocol is RS232 asynchronous serial or IrDA Physical Layer, if the infrared port is used. The data flow is half-duplex [4].

The parameters of serial communication for the infusion pump:

- Baud rate: 38400 bit/s
- Data bits: 8
- Start bit: 1
- Stop bit: 1
- Parity: none

- Flow Control: none.

The connector used for data transmission is a male DB9. The connector configuration is presented in figure 2.34:

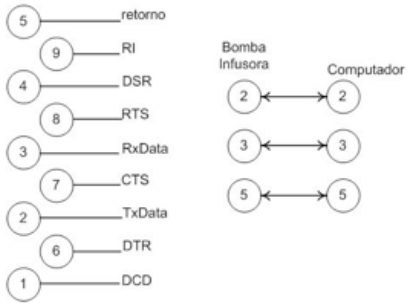

Figure 2.34: Connector configuration DB9, male Asena.

The communication protocol provided by the manufacturer [4] establishes a structure of data frames to exchange data. The actuator is the critical component in a TCI system, since errors from this component can represents from a fatal overdose to a fail in the drug titration causing awareness with several subject damage.

The data frame is composed by: the start bit, the command, a delimiter, CRC and the stop bit. The CRC used in the communication protocol is a CCITT, where the error average is less than 0.0015%.

The implementation of the communication protocol follows the stages:

- CRC: the code of CRC CCTI for 16 bits was provided by the manufacture. However, the code was first implemented in LabView with a C++ library and, later, the entire code was translated to a schematic language. The first tests with the CRC code did not present any errors but the implemented CRC was only approved for usage as the infusion pump driver after several tests were performed with all codes in the user guide

- Serial number: the serial number of the infusion pump is the key to control the equipment. The data frame access is allowed by a code composed basically by the

serial number. This number is encrypted and sent from the computing system to the infusion pump to start the communication.

- Command access: To ensure the infusion pump is on and communicating without errors, the computing system must receive and send an access command every 10s. This access command maintains the communication between the infusion pump and the computing system. If its transmission fails, an alarm sound is triggered, ending data transmission and any action of the infusion pump with the subject. This command includes the encrypted serial number, to validate the correct pump is being controlled. Any command from the computing system to the infusion pump follows immediately after the transmission and reception of the access command.

- Command: after the implementation of the access command, around 130 commands from the user guide were tested as commands from the computing system to the infusion pump and vice-versa.

The implementation of the stages described above allowed the complete control of the infusion pump and the development of a generic driver for infusion devices considering infusion errors, security routines, alarm routines, log history, etc. The drivers for clinical use revealed a high level of reliability and robustness.

The communication protocols implemented during this study demonstrated critical and specific conditions to be used and held in a clinical environment. The algorithms for detection and correction of errors, the frame data structure specific for each equipment enrich the final result as a TCI system, ASYS.

Chapter 3

Anaesthesia Synchronization Software - ASYS

Sueña y seras libre de espiritu, lucha y seras libre en la vida. - Ernesto Che Guevara (Physician)

Introduction

This chapter presents the software development process (SDP) of the Anesthesia Synchronization Software (ASYS). The SDP of a software normally follows a process model repeatable and predictable to guarantee the improvement of productivity and quality. The oldest and more common SDP model is the waterfall model composed of the following activities [55]:

- Requirement specification;
- Design;
- Implementation;
- Integration;
- Testing;

- Installation;
- Maintenance.

The SDP of a TCI system was not described in the literature. Therefore the SDP of ASYS started with intense research of how the TCI system could be idealized, designed, implemented, tested and validated for clinical use. The chronology of development that conducted to TCI systems is represented by the time line show in figure 3.1:

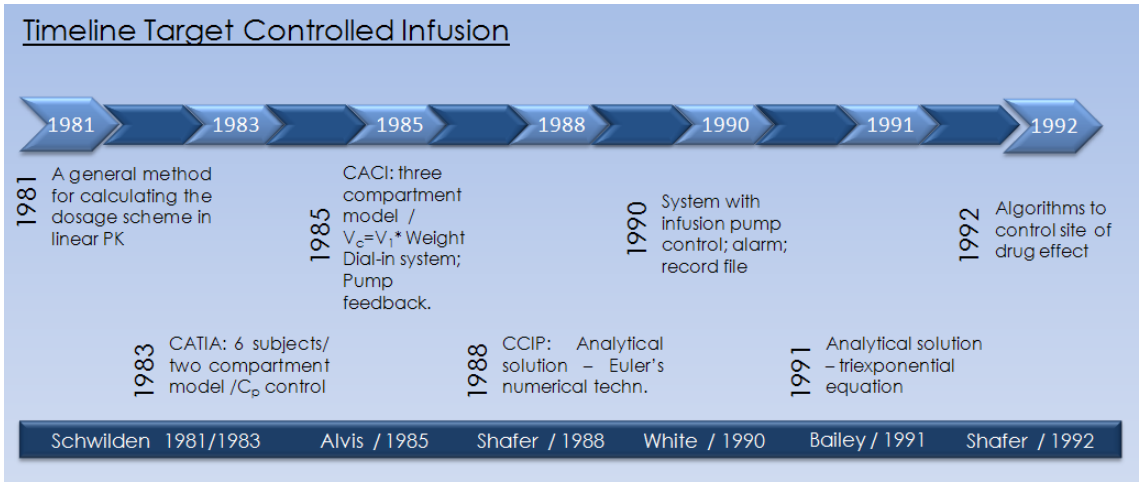

Figure 3.1: Target Controlled Infusion Systems Time Line.

In the requirement specification phase of SDP of a TCI system two initial questions were present:

1. *How to infuse into a compartment "'i"' to achieve a prescribed time course of amount of drug in compartment "'j"'?*
2. *What drug dose must be infused per time to keep a steady state concentration?*

Considering a two-compartment pharmacokinetic model, Schwilden in 1981[56] answered these two questions presenting a dosage scheme governed by a rule that administers a bolus to produce a blood level, followed by a maintenance infusion rate to

replace the constant amount drug transfer per unit of time, as demonstrated at 3.2 :

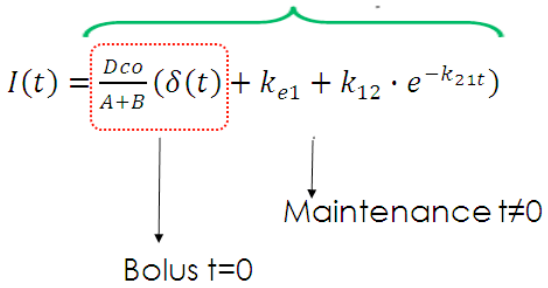

Figure 3.2: First equation by Schwilden to achieve a desired concentration.

The Schwilden paper should be enough to clarify the first questions in the design of a TCI system, however a third question may arises during the development:

What drug dose must be infused to provide a constant therapeutic action in the subject?

Schwilden, in 1983 [21], answered this question updating his first dosage scheme, now considering the "termination of drug effect" and the "elimination process" of the anesthetic.

The dosage scheme presented by Schwilden became known as "Bolus, Elimination and Transfer" or simply BET. The BET scheme became the base of all schemes, methods or algorithms for drug delivery of continuous intravenous anesthesia. A (B)olus to fill the central compartment followed by a constant infusion rate to replace the drug (E)limination and the (T)ransfer between compartments was adopted as an effective method to solve the drug delivery problem expressed in a finite sequence of steps.

Knowing how to infuse a drug to achieve a concentration in the subject, still leaves the problem of how to do it in the clinical setting. Manual implementation of

BET is complex, so a new question arises: *How to implement BET as a list of well-defined instructions to command an infusion device to titrate anesthesia?*

The first step to translate the BET scheme into a computing language is to translate the physicians actions into steps for solving a given class of problems, in this case administration of intravenous anesthetics. For intravenous anesthetics this is usually done by changing the speed of an electrical pump or the flow rate of a gravity driven intravenous solution in drops/minute, ml/h or mg/kg/h.

Alvis in 1985 [57] presented the Computer-Assisted Continuous Infusion (CACI), demonstrating how to translate the physician action, into commands to an infusion device. CACI used two equations to accomplish the desired concentration; the additional loading dose (ADDL) or bolus and the maintenance infusion rate. The ADDL equation introduced also an improvement in the calculus of the volume of the central compartment considering the subject's weight. This brought accuracy to the drug dose titration and increased the reliability of the system.

The results of Alvis's study led to a version of CACI closest to the current TCI systems. A "dial in" software enables the physician to set a target for plasma concentration, estimates the predicted concentration in the subject and places the physician as a decisor of the drug delivery system.[22]

The steps taken by the physician to deliver intravenous anesthesia translated into a program code evoke safety questions, since the system is intended for clinical use, this brings another question: *How to guarantee the accuracy of the specific implementation of the pharmacokinetic model in the system and the accuracy of the device?*

Any application running in a computing system implies that data are discrete-time, since a computer program code work with discrete points of time. According to

this, the pharmacokinetic model implementation must be introduced in the algorithm as a discrete time system.

Shafer in 1988 [23] published a set of tests to evaluate TCI systems in simulation mode prior to clinical trials, presenting for the first time, an analytical solution with a discrete time system of the three-compartmental pharmacokinetic model. After performing the set of tests, Shafer concluded that the Euler numerical technique used for approximating the differential equations performed accurate by using a sampling time above 15s.

The Euler's method applied by Shafer or the bilinear Z-transform used by Alvis were approximations of the exact solution to the three-compartmental model, however the simplest solution adopted by several known TCI systems were presented by Bailey. In ASYS a novel controller was developed, it uses the Zero-Order-Hold (ZOH) method.

In the SDP a third question of implementation need to be answered: *How to control and achieve the desired concentration at the site of drug effect?*

Pharmacokinetic models were developed based in plasma were measurements and so they modelled to predicted plasma concentration. However, it became well known that what accounts to the effect of intravenous anesthetics is the drug amount in the effect site, that is the brain. Brain concentration can not be directly measured as plasma concentration, however the effect of intravenous anesthetics in the brain became easily measurable using EEG derived parameters. This allowed researchers, to improve PK models to include the predicted of effect-site or brain measurements. This led to the additional needs of TCI systems to control including an effect-site compartment in the algorithms.

Shafer in 1992 [17] presented the solution with an algorithm to control the effect-site concentration. The authors started by reformulating the mammillary model including an effect-site compartment as a four-compartmental model and changing the mathematical terms in amount of drug. After the change for pharmacokinetic and pharmacodynamic model, the authors pointed the goal of the algorithm: the inclusion of this fourth compartment or biophase allowed the system to reach and maintain the target concentration at site of drug effect rapidly as possible without producing overshoot.

Shafer's study provided two solutions to control the effect-site concentration: the first used an algorithm with Euler numerical; it may be intuitive, simple and computationally undemanding; the second solution was analytical used continuous forms of the simple difference equations but, only solved by numerical techniques at that point. Since the technology advance enabled the second solution to be implemented and used by several known TCI systems, including ASYS.

This chapter shows how these five questions were answered and implemented in the development of ASYS.

3.0.4 Implementation of PK/PD model in ASYS

The Implementation phase of the SDP was preceded by the requirement specifications and the system design. These two phases were addressed by the five questions and answers in the introduction of this chapter. The development of ASYS started with the implementation of the communication protocol described in chapter 2, and followed by two other steps: a partial implementation with the PK/PD model and infusion device driver, and the complete implementation of the Infusion Rate Control Algorithm (IRCA) of the TCI system. The complete program that led to ASYS is represented in figure 3.3.

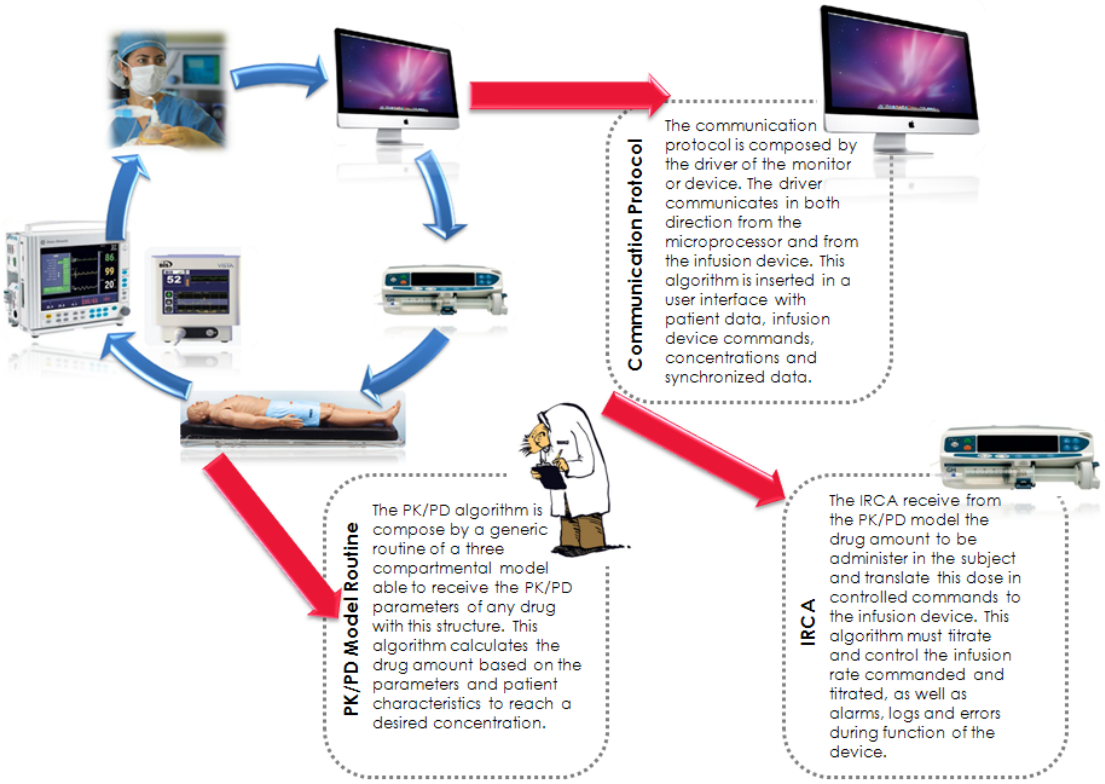

Figure 3.3: Phases of development of ASYS.

Intravenous anesthesia uses an hypnotic, an opioid and a muscle relaxant. For the model commonly used to design each of these drugs the pharmacokinetics are well described by a three compartment model [14],[58],[59]. Therefore, the first step for the development of TCI system was the implementation of a three compartment PK/PD model.

The algorithm implemented in ASYS is such that it can receive the PK/PD parameters of any new three compartmental model introduced by the user or open a file with specific PK/PD model previously recorded. Figure 3.4 shows the PK/PD interface of an ASYS's routine:

The next step in programming of a TCI system should be the mathematical manipulation of the differential equations in discrete time. However, some of the PK/PD models have its parameters based on the subject's data: weight, height, age and gender [20], [58] , [59]. This brings into consideration a relevant issue in TCI systems, does size matters? [60]

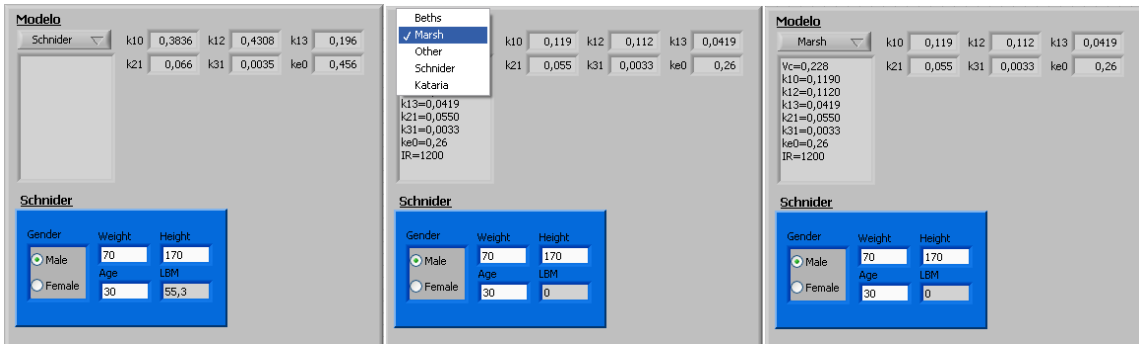

Figure 3.4: Interface of PK/PD model option and configuration.

Egan [61], Bouillon [60] and recently by Absalom [11] questioned the influence of weight in the PK/PD model and consecutively in the drug dose titrated. Egan studied the pharmacokinetics of the opioid remifentanil in twelve obese subjects in comparison with lean subjects. The author found that the absolute volumes and clearances between obese and lean subjects are similar and that the use of total body weight (TBW) for drug titration was wrong. The study demonstrated that the drug dose of remifentanil was more closely related to the ideal body weight (IBW) or to the Lean Body Mass (LBM) TBW.

There are formulas for the calculating of lBM Egan's study used James's formula [62]:

Male:

$$LBM = 1.1 \cdot weight - 128 \cdot \left(\frac{weight}{height}\right)^2 \tag{3.1}$$

Female:

$$LBM = 1.07 \cdot weight - 148 \cdot \left(\frac{weight}{height}\right)^2 \tag{3.2}$$

Commercial devices are currently widely available for TCI anesthesia and the way such devices approach the weight is very important.

Absalom in his own words "defined and illuminated the devil" [11], addressing the pharmacokinetics of the propofol models. He clearly explained how the system should control plasma and effect-site concentration and defined the methods for the estimation of k_{e0}. This paper clarifies the changes between plasma and effect-site compartment as well as estimate the time of course in the effect-site compartment.

The most widely used PK/PD models for propofol are the ones from Marsh [19] and Schnider [20], which are implemented in the TCI commercial devices. Absalom [11] compared the two models and pointed out their differences in terms not only of their classical PK parameters but also in the way were conceived. Besides comparing the two models Absalom addressed the question of the difference in the drug administration in lean, obese and severely obese subjects. The author highlight the difference in using LBM, IBM or TBM.

The issue related with the use of the equations 3.2 and 3.1 become a problem when extremely obese patients are taking in count; with the increases of weight the LBM decreases, as presented in figure 3.5, turning to a negative value. During the implementation of TCI software this paradox issue must be consider and a strategy adopted to be used with extremely obese and obese patients.

A possible solution to this is using simply the subject's weight as it is done with Marsh's model. However, when using Schnider, which take in account LBM, one has to implement an different solution, namely limiting it's use to a value of LBM. For the Fresenius system the limit of IBM is below 35. For ASYS the limit is based on LBM, the user must insert a value of body weight below the maximum LBM, according to the law represented in figure 3.5.

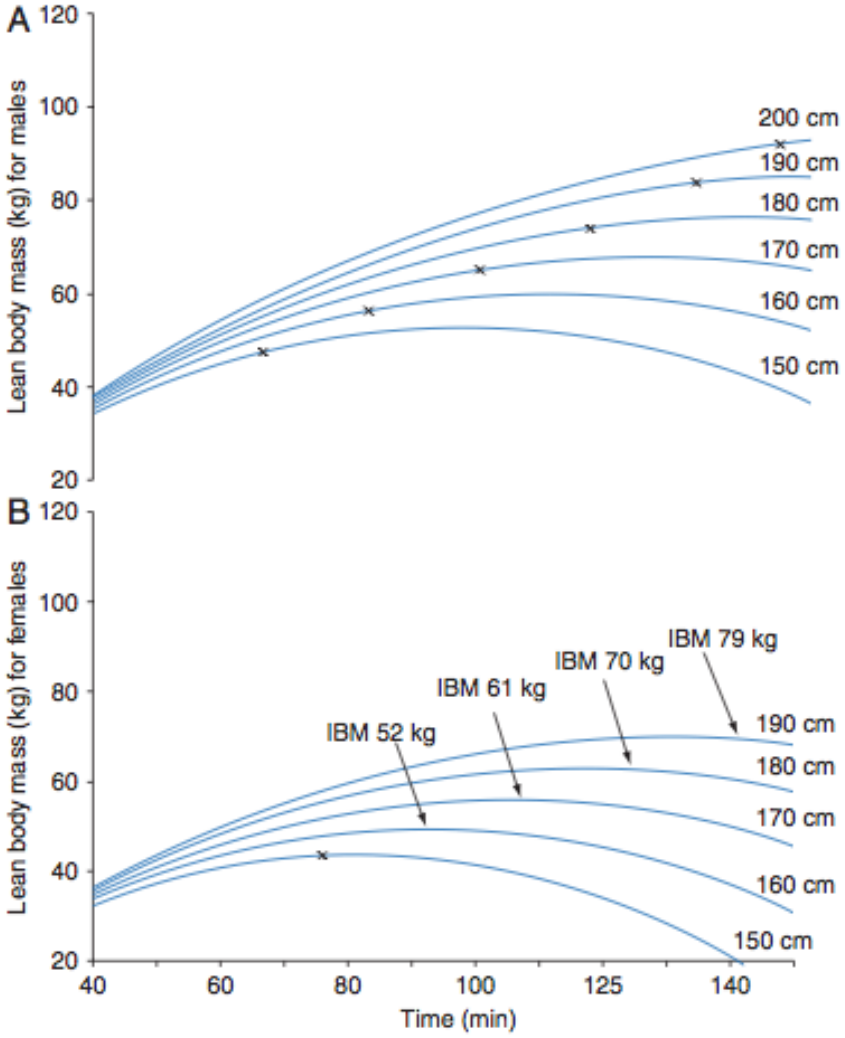

Figure 3.5: Graphic adapted from Absalom study [11], presenting LBM for males (A) and females (B).

ASYS has implemented a Marsh model with $k_{e0} = 0,26 min^{-1}$. The Marsh model is not indicated to be used in the induction of anesthesia of severely obese subjects.[11]

When the PK model by Schnider [20] is used to administer the hypnotic propofol, the PK parameters V_1, V_3 are fixed while V_2 is influenced by age. By the rate constants, the elimination rate constant k_{10} is the only one influenced by the body mass. The equation to calculates k_{10} in Schnider model follow:

$$k_{10} = 0.443 + 0.0107 \cdot (weight - 77) - 0.0159 \cdot (LBM - 59) + 0.0062 \cdot (height - 177) \quad (3.3)$$

The LBM adopted to calculate k_{10} was 3.2 and 3.1.

The elimination rate constant is very important, namely during the maintenance of steady state: in this phase the amount eliminated is equals to the drug amount administered. However the use of the LBM in the equation 3.3 opens a paradoxical question between the LBM and the TBW. To solve this paradox, ASYS has a routine, figure 3.6, that is activated when Schnider model is used considering the Total Body Weight (TBW) and the curve presented in figure 3.5. When the user inserts the patient's weight and height to calculated TBW and LBM, an algorithm analysis the value considering the curve from figure 3.5, if the values falls on the declining portion of the curve, the user is requested to insert a valid or a value between set limits of LMB.

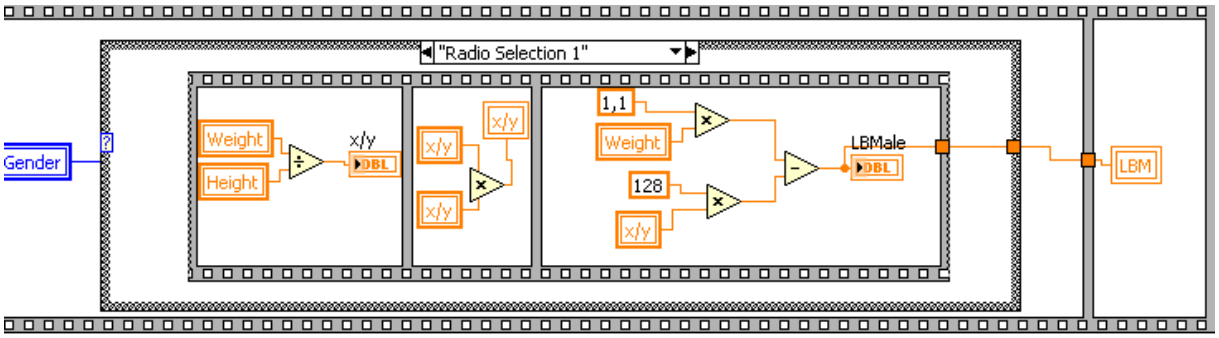

Figure 3.6: LBM routine for PK/PD model.

When the Schnider model is used, the estimation of the effect site concentration can be done in two ways: by a fixed k_{e0} or by the individual adjustment of time to peak effect. ASYS was implemented with a fixed $k_{e0} = 0.456 min^{-1}$, establishing different TTPE for different subjects.

The routine related to the subject data are very important in the develop-

ment of a TCI system, namely in the design of the routine used for the user to insert the subject data.

The next step of partial implementation is the mathematical manipulation of the system with the differential equations (3.12, 3.13, 3.14, 3.15). The algorithm considers the PK/PD parameters described above and discrete in time the system, using the Zero-Order-Hold method. The programming language used was LabView by National Instruments. The logic block used to discrete the system implements automatically a system model in discrete state-space form with sample time, input and output as graphically presented in figure 3.7:

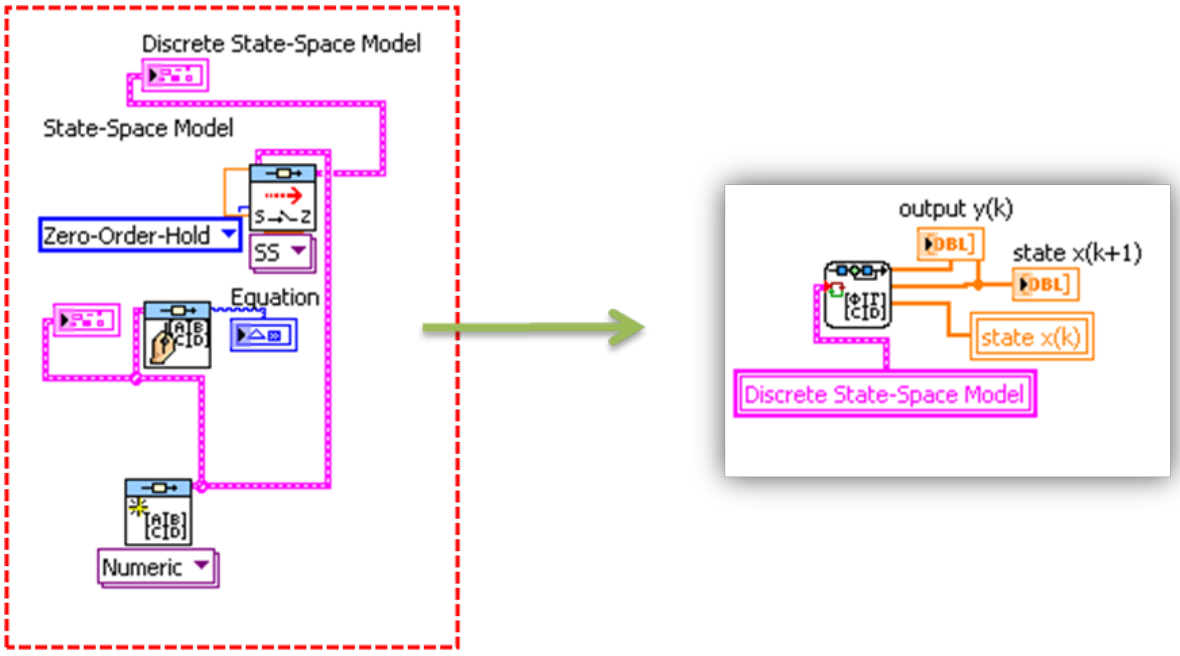

Figure 3.7: Partial logic of discrete the continuous PK/PD model.

The output of the discrete state space function is used to estimate the plasma and effect site concentrations every 10s. These estimated concentration are used in the IRCA by the optimal controller, discussed in the section Bolus, Elimination and Transfer Scheme - The Controller.

The partial algorithm composed by communication driver, PK/PD generic algorithm and some commands as bolus and constant infusion rate, as in figure 3.8, was tested and validated to the next stage - the controller.

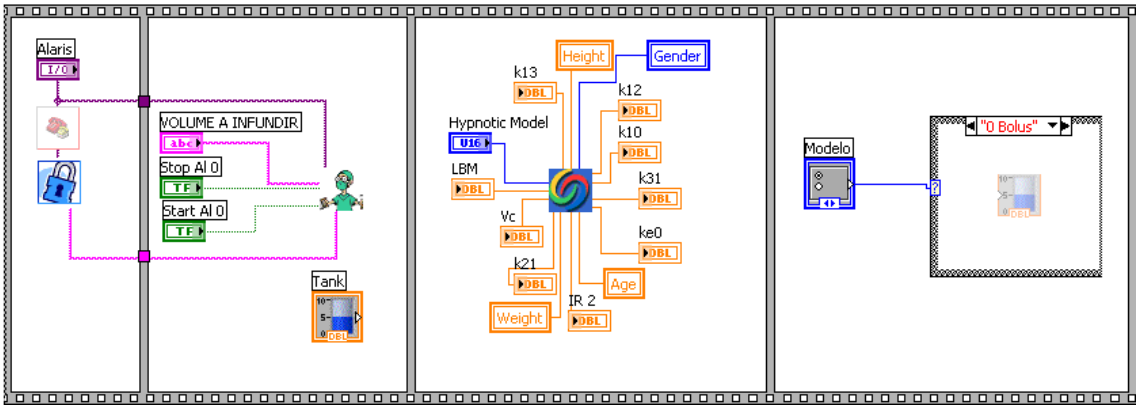

Figure 3.8: Partial logic with driver, PK/PD model and infusion device commands entry.

3.1 Implementation of TCI Controller in ASYS

TCI systems are composed of two algorithms: the PK/PD model, to simulate drugs behaviour and estimate the site concentration; and the Infusion Rate Control Algorithm (IRCA), used to command the infusion device to titrate the amount of the drug following the PK/PD estimatives.

Consecutively, IRCA is based on the Bolus, Elimination and Transfer scheme (BET) [21] aiming at rapidly achieving the target concentration (C_T) and maintaining it without overshooting. The BET scheme accomplishes this goal with a vector of infusions. It starts with a fast infusion, called bolus, to fill the central compartment and rapidly achieves the desired C_T, this is then followed by a continuous infusion to replace the drug leaving the central compartment either by elimination to the outside and drug transfer to peripheral compartments [63]. The structure of an IRCA is based on the BET concept, so that algorithms always have to be based on bolus and maintenance concepts.

The first sketch of an IRCA was put forward by Kruger-Thiemer [64], it was based on bi-compartmental PK model with only three PK parameters. In this dose scheme the "'exact plateau effect"' should be achieved by a initial optimal dose $I(0)$ followed by continuous infusion decreasing with time.

$$I\left(0\right) = LD \cdot \left(k_{12} + k_{13}\right) \tag{3.4}$$

$$I(t) = LD \cdot \left(k_{12} + \sum_{v} k_{1v} exp\left(-k_{v1 \cdot t}\right) \right) \tag{3.5}$$

Where:

LD: optimal initial dose

k_{12}: first order rate constant for renal excretion

k_{13}: rate constant out of "'plasma water"'

This dose scheme was developed to be used with PK models with any number of compartments. However, 10 years later Schwilden [56], presented a general scheme for a PK bi-compartmental model implemented in a microprocessor 6502 which was tested on 12 subjects. It was based on the following equation:

$$I(t) = \frac{Dc_0}{A+B} \left(\delta(t) + ke_1 + k_{12} \cdot e^{-k_{21}t} \right) \tag{3.6}$$

Where A, B are functions of the transfer constants k_{e1}, k_{12} and k_{21} and D is the dose. At t=0, a bolus was titrated by term $\delta(t)$; and at $t \neq 0$ the drug replaced by $\frac{D_{c0}}{A+B} \left(k_{e1} + k_{12} \cdot e^{-k21t} \right)$ representing the maintenance phase.

During the 1980's, several research groups developed controllers for plasma concentration, such as Alvis [57], with an algorithm composed of three device rules and two infusion equations:

1. Rule 1: $C_{pT} > C_p$: To increase plasma concentration from C_p (actual plasma concentration) to C_{pT} (new plasma concentration target), a bolus must be commanded to the infusion device to fill the central compartment, calculated by equation 3.7.

$$ADDLD = (C_{pT} - C_p(t)) \cdot V_1 \tag{3.7}$$

To keep the plasma concentration and to compensate the transfer between com-

partments as well as the elimination from the central compartment, a constant infusion is titrated by the infusion device, calculated by equation 3.8:

$$I(t) = C_{pT} \cdot V_1 \left(k_{10} + k_{12} \cdot e^{-k_{21} \cdot t} + k_{13} \cdot e^{-k_{31} \cdot t}\right) \tag{3.8}$$

2. Rule 2: $C_{pT} = C_p$: To maintain plasma concentration at same target the equation 3.8 is recalculated every $10s$ based on the PK model and titrated by the infusion device to the patient.

3. Rule 3: $C_{pT} < C_p$: To decrease plasma concentration the infusion device is stopped until the target concentration is reached. The infusion device titrates a constant infusion during the maintenance by equation 3.8.

Those controllers were developed to control the plasma concentration using numerical solutions based on BET scheme. However, Jacobs [65] at the end of 1980's presented an analytical solution of IRCA to control C_p. The method was implemented and tested in a computed-aided system resulting in a robust algorithm It was not vulnerable to aliasing and accurate, but mathematically too complex to be applied in real time computed-aid systems.

Later Bailey [27] improved Jacobs analytical solution simplifying the control of C_p, optimizing the algorithm's performance and reducing the infusion rate to simple equation. Bailey state that the plasma was not the site effect for most of the drugs, pointing to a controller need to developed for effect-site concentration. Shafer [17], in 1992, using the same analytical solution of Jacobs, approached the control of effect-site concentration and presented a new algorithm for computer-controlled infusion pumps.

This algorithm [17] is still currently in several known TCI systems, as Rugloop©[35]. It demonstrated the ability to target the site of drug effect easily achieving and maintaining the target concentration without overshoot. However, Shafer highlighted the fact that a high C_p peak might result in toxicity, considering that the drug can have a different site for toxicity effect other than the therapeutic site. Therefore, Shafer suggested the inclusion of a constrain in the algorithm.

Poucke [66] addressed these issues and modified Shafer's algorithm limiting, C_p by the equation 3.9:

$$I_{lim} = I_{exact} \cdot \frac{C_{pLIM}}{C_{pMAX}} \tag{3.9}$$

Where I_{exact} limits the infusion rate to reach C_e target:

$$I_{exact} = \frac{C_{eT}}{C_{eU}} \tag{3.10}$$

C_{pMAX} is the peak C_p after I_{exact} has been titrated.

C_{pLIM} must be set in a value $\leq C_{pMAX}$.

C_{eT} is the target concentration in the effect site.

C_{eU} is the concentration in the effect site at TTPE.

The results of Poucke's mathematical algorithm presented reductions at peak C_p up to 60% with a "modest effect" on the effect-site concentration.

In the same year 2004, Ting [67] introduced a close-loop controller for anesthesia. This study also presented a new equation (3.11), for open loop control.

$$I(t) = \delta(t) \cdot LD + \left\lfloor k_{10} + k_{12} \cdot e^{k_{21}t} + k_{13} \cdot e^{k_{31}t} \right\rfloor \cdot LD - \left\lfloor k_{21} \cdot x_2(0) \cdot e^{k_{21}t} + k_{31} \cdot x_3(0) \cdot e^{k_{31}t} \right\rfloor \tag{3.11}$$

Where x_2 and x_3 are the volume at compartments V_2 and V_3.

The difference in this dose scheme was the inclusion, in the infusion rate equation, of the initial volumes of the second and third compartments.

With time, a consensus was generated, so that the most widely used controller for anesthesia with open loop TCI was the one based on the analytical solution. Careful study of this systems and their evolution, and specially the analysis of Shafer and Pouckes's algorithms, led to the pursuit of possible improvements in TCI system, namely in the development of its controllers. Such development should limited C_p, without overshoot the effect-site concentration, decreasing the time to reach the target and decreasing the drug amount titrated.

3.1.1 Novel Infusion Rate Control Algorithm

The concept of TCI lies on the PK/PD model and its mathematical approach of the drug/body behaviour during anesthesia, including the drugs's effect site to achieve this, where the fourth compartment represents the effect compartment or the biophase of the drug.

The rate constants from the PK/PD model were used to determine the infusion rate and the maintenance infusion required to reach the target plasma concentration (C_{pT}) and target at site effect C_{eT}. The initial infused volume is proportional to V_1. The elimination rate was determinant variant to keep the target concentration (C_T). C_p and C_e were estimated based on model interaction, described in previous

pharmacokinetics/pharmacodynamics studies, for given populations.

The three-compartment model with an effect-site compartment can be described by the following differential equations (3.12, 3.13, 3.14, 3.15) published by Poucke [66]:

$$\begin{aligned}\frac{dC_1(t)}{dt} &= -(k_{10}+k_{12}+k_{13})\cdot C_1(t) \\ &\quad +k_{12}\cdot C_2(t)+k_{13}\cdot C_3(t)+\frac{I(t)}{V_1}\end{aligned} \tag{3.12}$$

$$\frac{dC_2(t)}{dt} = k_{21}\cdot(C_1(t)-C_2(t)) \tag{3.13}$$

$$\frac{dC_3(t)}{dt} = k_{31}\cdot(C_1(t)-C_3(t)) \tag{3.14}$$

$$\frac{dC_e(t)}{dt} = k_{e0}\cdot(C_1(t)-C_e(t)) \tag{3.15}$$

Where C_1, C_2, C_3 and C_e are the concentrations in each of the different compartments. I is the infusion rate in ml/h. Based on these equations the systems can be modelled by a conventional state space approach:

$$\dot{X}(t) = A \cdot X(t) + B \cdot I(t) \tag{3.16}$$

$$C_p(t) = C \cdot X(t) \tag{3.17}$$

Where:

$$A = \begin{bmatrix} -(k_{10} + k_{12} + k_{13}) & k_{12} & k_{13} & 0 \\ k_{21} & -k_{21} & 0 & 0 \\ k_{31} & 0 & -k_{31} & 0 \\ k_{e0} & 0 & 0 & -k_{e0} \end{bmatrix}$$

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

$$C = \begin{bmatrix} 1 & 0 & 0 & 0 \end{bmatrix}$$

$$X(t) = \begin{bmatrix} C_1(t) \\ C_2(t) \\ C_3(t) \\ C_e(t) \end{bmatrix}$$

Considering the matrix rule described above from Poucke's study [66] we developed a new controller [68] to be used in our TCI software Anaesthesia Synchronisation Software (ASYS) [69]. Figure 3.9 illustrates the diagram block of the IRCA:

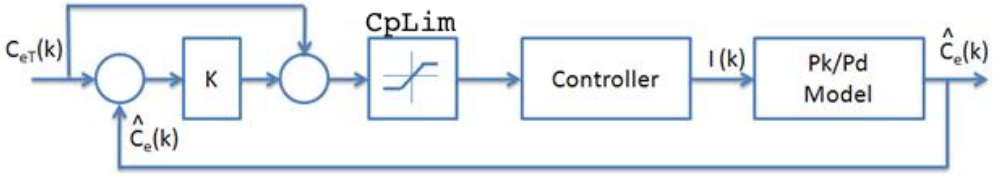

Figure 3.9: Control diagram with new controller.

Where:

- K: proportional gain adjusted to avoid overshoot and with optimal steeling time. In a future development, this gain will be adjusted in a future based on the LBM and C_{pLIM}.
- C_{pLIM}: is not necessary set as a constant value. The constrain can be calculated using several different equations , as for example the equation 3.18 published by Poucke[66]. This IRCA limited C_p avoiding an overdose or toxicity.

$$R = \frac{C_{pMAX} - C_{pLIM}}{C_{pMAX} - C_{eT}} \tag{3.18}$$

- Controller: represented by equation (3.21) without set the constrain C_{pLIM}.
- Pk/Pd Model: depends on user selection. Available propofol: Marsh [70], Schnider [20], Kataria [71], Beths [72], for remifentanil Minto's model [58].
- $C_{eT}(k)$: effect site concentration target
- $I(k)$: infusion rate [ml/h]
- $\hat{C}_e(k)$: estimated effect site concentration.

Therefore, considering the continuous model, the Zero Order Hold method was used to discrete the continuous space state model (time invariant), as follows:

$$X(k+1) = F \cdot X(k) + G \cdot I(k) \tag{3.19}$$

$$Cp\,(k) = H \cdot X\,(k) \tag{3.20}$$

Consequently, without the limit on the constraint CpLIM, and equalizing the state space model in order to the input I(k) the infusion equation is as follows:

$$I\,(k) = [0.36 \cdot inv\,(H \cdot G)] \cdot \left(K \cdot \left(\frac{\frac{C_{eT} - X(4)}{V_1}}{1000} \right) + C_{eT}\,(k) \right) \cdot 1000 \cdot (V_1 - H \cdot F \cdot X\,(k)) \tag{3.21}$$

Equation 3.21 which represents a novel solution implemented in IRCA of ASYS instead of the traditional TCI algorithm. The use of a single equation to administer bolus and keep maintenance infusion (BET) was done, believing that such approach could improve computational performance of the system.

3.1.2 Optimal Control Algorithm

The system described by (3.12, 3.13, 3.14, 3.15) and the PK/PD parameters k_{ij} were introduced in programming language called A Mathematical Programming Language (AMPL). This algebraic modelling language allows we to solve problems of linear or non linear optimization, in continuous or discrete variables, using specific mathematical solvers.

AMPL can be described as a text editor where the non linear problem was introduced, however, another algorithm called KNITRO, was used to read the file and optimize the gain K, represented at figure 3.9.

Knitro is a solver to be used by mathematical software to compute numerical solutions to optimization problems composed from standard Mathematica functions. Knitro is designed to finding local solutions of large-scale, continuous nonlinear problems. Therefore, the KNITRO solver [73] reads from the AMPL file, the follow parameters:

1. The Input Parameters:
    - patient data: weight, height, gender and age;
    - initial values from Vn, C_p and C_e;
    - the system matrices A, B, C, D;
    - k_{ij} based on the PK/PD model chosen and
    - the C_T in the specific site (plasma or effect).
2. The Constrains:
    - C_{pLIM};
    - Infusion rate limit of the infusion device (between 0 and 1200ml/h);
    - $C_{eLIM} = C_{eT}$;
    - $\frac{dC_{eLIM}}{d(t)} = 0$ with $t = t_{final}$.
3. The Cost Function: to minimize the time to reach the target (t_{final}).

Based on the system, the input parameters and constrains, the KNITRO algorithm calculates the optimal input and generates the optimal curve. The KNITROs algorithm solves the optimal problem using three different algorithms: the Interior/Direct; the Interior/CG and the Active set, which are not described in detail in the literature (private from Ziena Optimization)[74]. Figure 3.10, shows the optimal infusion rate curve to rapidly achieve a $C_{eT} = 3ug/ml$ in a 50kg male subject using Marsh's model:

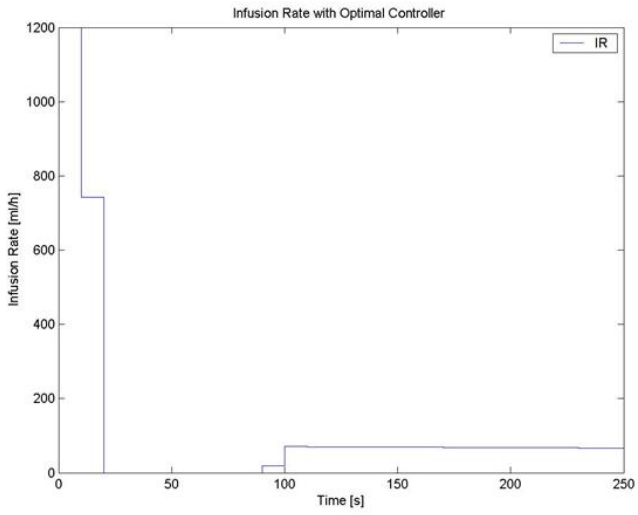

Figure 3.10: Optimal Infusion Rate - KNITRO

Figure 3.11 shows the corresponding effect-site concentration without overshoot, as follows:

Considering the optimal curve for the infusion rate to reach the target, figure 3.11, and the curve from the actual controller to reach the same target, the absolute error is given by the absolute difference between the two curves. Based on this absolute error the algorithm calculates the optimal K that minimizes the absolute error sum (3.22).

$$errorsum = \sum_{i=1}^{n} abs\left(C_{eOPT}\left(i\right) - C_{e}\left(i\right)\right) \tag{3.22}$$

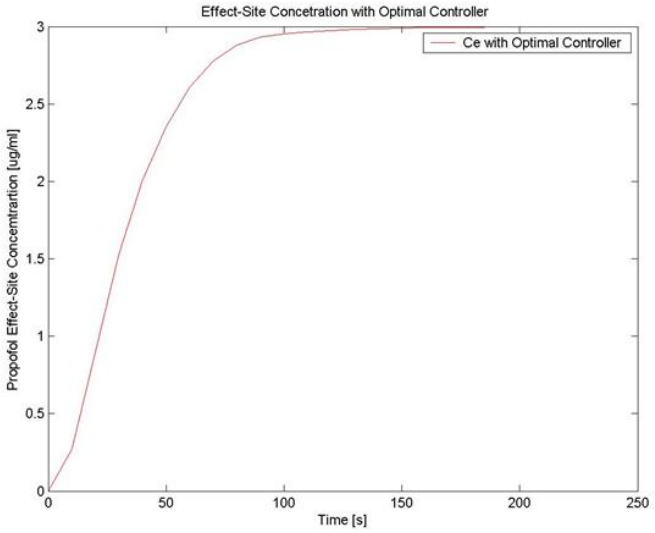

Figure 3.11: Optimal Effect-Site Concentration from the Optimal Infusion Rate - KNITRO

The optimal K implemented in the IRCA of ASYS generates a similar curve to the optimal curve generated by KNITRO, as figure 3.12:

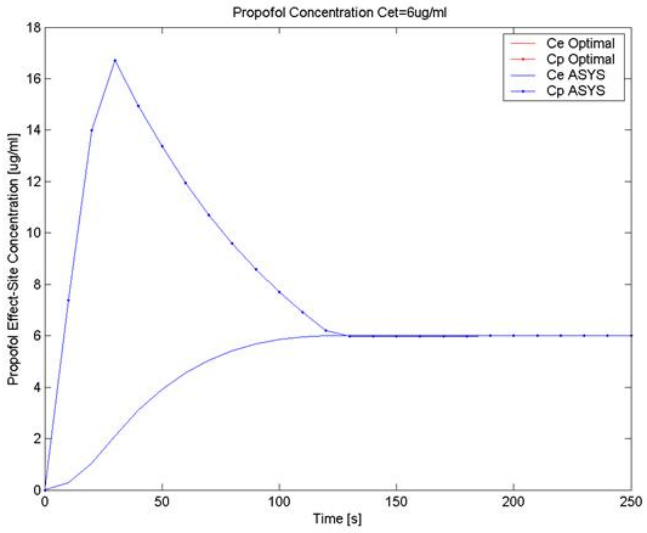

Figure 3.12: $C_{eT} = 6ug/ml$ with Schnider model, 90 year old male, 70kg weight and 170cm height - Optimal curve from KNITRO and Optimal Algorithm implemented at IRCA of ASYS.

3.2 Driver Total Implementation - ASYS

3.2.1 How do Infusion Rate Control Algorithm work?

When the physician specifies a C_T (plasma or effect) in a TCI software, the PK/PD model uses an algorithm to convert, the concentration into a drug dose (ml). This drug dose is the input of the controller of the IRCA.

The controllers goal is to rapidly achieve the target without overshoot, following the BET scheme. The IRCA uses the result from the controller, as infusion rates, to drive the infusion device. It also checks if the exact drug dose was correctly administrated and the possible occurrence of faults.

This cycle must be executed in $10s$, because this is the the sample time of the PK/PD model estimated. After $10s$ the IRCA compares the C_T with the estimated concentration by the PK/PD model and the cycle restarts.

The functions of the IRCA are to control the drug dose to be administrated and assure the right amount is delivered keeping a safe and accurate communication with the infusion device. The time used to control and communicate with the infusion device could be the key to improve IRCA performance.The faster and more frequent a system could check the status of the pump and the PK/PD estimates the better it should perform to correct the drug administration and concentration.

The novel IRCA proposed and implemented in ASYS aimed at optimized the controller reducing time and improving algorithm performance in three steps:

1. The BET scheme as bolus and maintenance is performed by one equation 3.21: Simplifying the algorithm to one equation may reduce the margin of error arising from the computational manipulation of data and optimize the performance of the software.

2. Maximize the optimization of the BET equation 3.21 with an optimal control

algorithm:

An optimal algorithm using KNITRO solver was developed to optimize the gain K. This optimization aims achieve the best infusion rate to achieve a specific C_T, at minimum time and without overshoot. This algorithm optimizes each individual infusion rate titrated till it reaches the target, reducing once more the cumulative error arising from the algorithm itself and from the computational manipulation of data.

3. Feedback:

Errors in TCI systems have been reported in several studies [22], [75], [76] related with positioning, dead space (infusion line) or with the pump mechanism. Errors result in a wrong amount of drug being administrated by the infusion device during a given period of time and in a delay in the control loop. This wrong amount is not considered by the algorithm or by the model which results in increased the error. The novel IRCA incorporates a feedback algorithm that controls the infusion rate commanded, the infusion rate administrated, and duration of administration.

The algorithm simplified the TCI algorithm reducing the controller to 1 equation. This improvement represents a better computational performance; it minimizes errors and reduces the complexity of the TCI systems, as a device or being computer-aided. The algorithm constraint that limits Cp could also be used to minimize the drug dose titrated. This option will increase the time taken to reach CeT considering the actual time, as Figure 10 demonstrates:

When the hardware technology was exhaustively explored, the simplification of the algorithm represented a way of improving the performance of the hardware. The first tests with the novel algorithm demonstrated a better computational performance

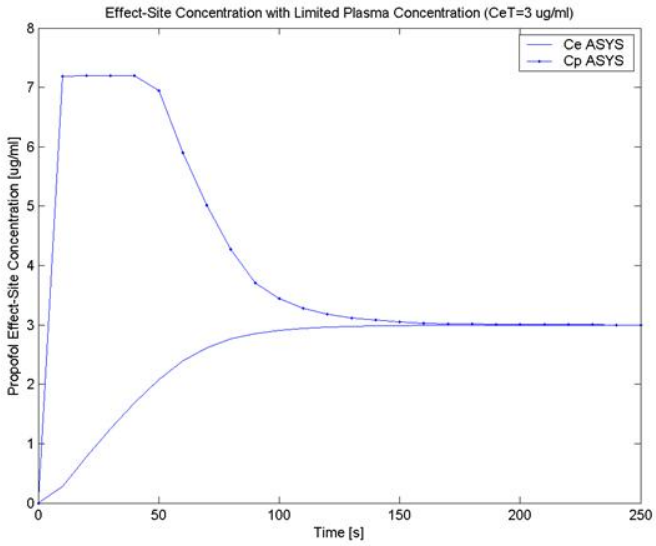

Figure 3.13: $C_{eT} = 3ug/ml$ with Schnider model, 30 year old male, 70kg weight and 170cm height - With $C_{pLIM} = 7.2ug/ml$ in the IRCA of ASYS

and none of the statistical tests presented errors. The IRCA accomplished the goal reaching rapidly the C_T without overshoot and follow the BET scheme eliminating errors from the algorithm and minimizing the errors from the infusion device.The novel IRCA represents a promising tool and is one step forward towards TCI engineering.

3.3 Uses of the Anaesthesia Synchronization Software - ASYS - In the Clinical Setup

3.3.1 ASYS - Versions of the software

UTAD

The final phases of a SDP, preceding the installation of a TCI software, integration and testing are required. The integration phase of ASYS started with the simplest configuration of a TCI software: one infusion device and one cerebral monitor, as figure 3.14:

This first version of ASYS was called ASYS Vet, since it was developed and tested at the Faculty of Veterinary from University of Tras dos Montes e Alto Douro

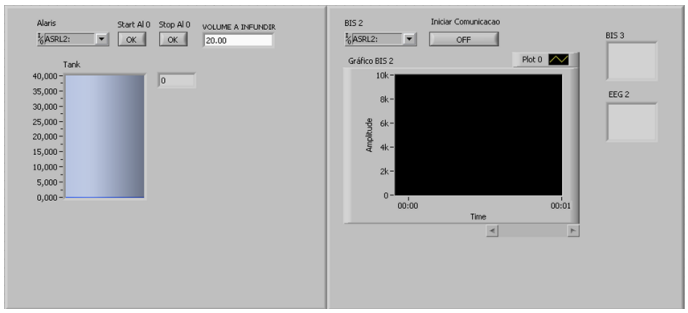

Figure 3.14: First Version of ASYS with BIS and infusion pump ASENA MK GHIII - Manual control.

(UTAD). The first version of ASYS Vet presented a BIS driver using the monitor model Bispectral Index XP and a driver for the infusion pump ASENA MK GHIII - Cardinal Health UK. The infusion pump driver was tested in this version for the very first time in manual mode, with start and stop command given by the user to administer a set drug dose. This version of ASYS tested the integration of two different drivers, BIS protocol communication had a 5s data sample while the ASENA had a 10s control and data sample, as follows in figure 3.15.

Figure 3.15: First Version of ASYS with BIS and infusion pump ASENA in clinical trial with a mice.

Laboratory tests evaluated the integration of both drivers and data synchronization. The first challenge was the fact that the infusion pump algorithm required 10s period for communication and control. The tests originated the first study of the IRCA:

the communication between computing system and the infusion device (read/write) must be done in 2s and the control (mathematical algorithm) in 8s. ASYS Vet in the first version, figure 3.16, captured, recorded and synchronized, data in a doc file format with time and date.

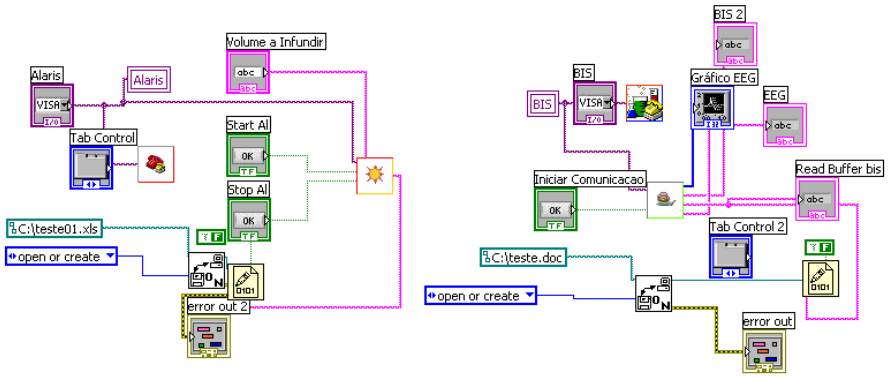

Figure 3.16: Routine of ASYS with BIS and ASENA driver.

A clinical trial with ASYS Vet was conducted at UTAD in three mice. Prior to anesthesia the mice were monitored with an adapted electrode of BIS, figure 3.17, that was developed by Bressan [69]. The mice were sedated with isoflurane and then cannulated at the abdominal region to administered propofol. it was then stopped and when the mice reached a value of BIS above 70, a continuous infusion of propofol was started until BIS decreased below 40; propofol was then stopped and the mice were allowed to recover. This implementation allowed improvements in the implementation of the pump driver.

The second version of ASYS implemented three different drivers: the cerebral monitor BIS, DATEX modular monitor and the infusion pump ASENA. In this version two infusion pumps were used, one for the hypnotic and one pump for the opioid remifentanil, as the scheme at figure 3.18:

The algorithm implemented three different protocol communications considering each protocol as an independent routine. The data was synchronized every 5s and recorded in a Excel- Microsoft spreadsheet automatically. The file was saved with the subjects individual data, date and time. This version two of ASYS Vet was developed

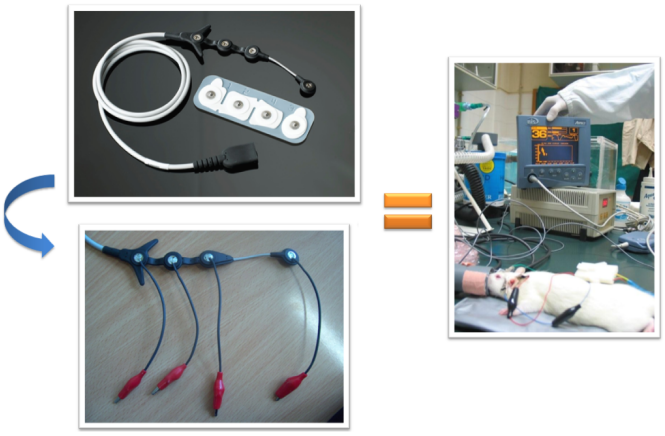

Figure 3.17: BIS adapted eletrode for animal use.

Figure 3.18: Device and monitors used at ASYS Vet second version.

using Baile [27] algorithm to control plasma concentration and a routine to administer a constant infusion rate. ASYS Vet version two was not tested in clinical trial.

King's College London

The next version of ASYS was called ASYSPK, a version developed to capture and synchronize data specially developed to meet the need of clinical researchers to be used at King's College London Hospital, as figure 3.19. This version implemented four different protocol communications: two ASENA PK, the LIDCO cardiac output monitor, BIS cerebral monitor and the INVOS cerebral oximeter. The infusion pump ASENA PK from Cardinal is a TCI system. The communication protocol of an ASENA PK transfers the pharmacokinetic/pharmacodynamic data from the infusion device to a

computing system as backup or a record system.

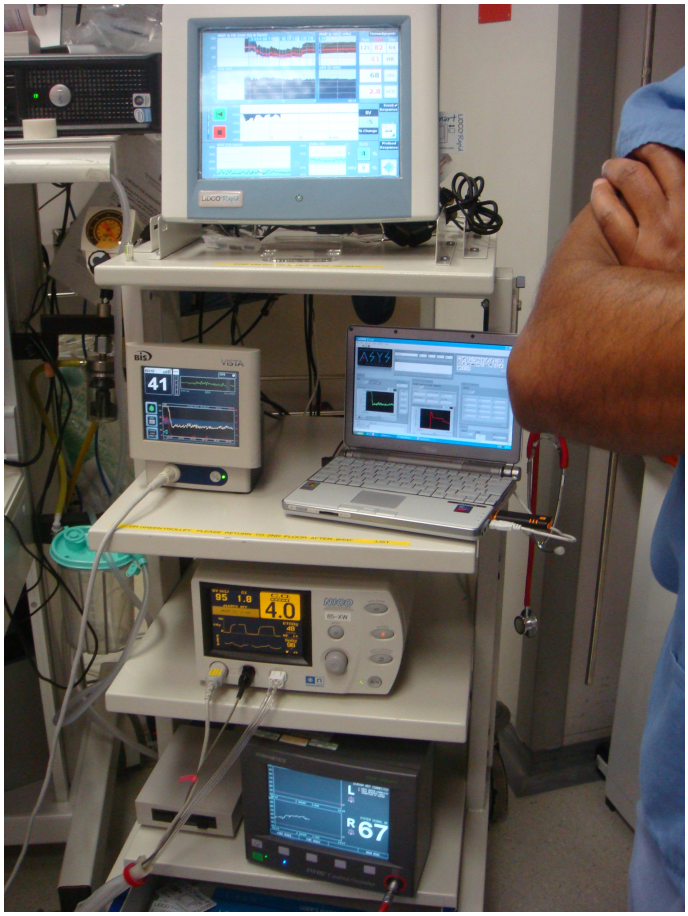

Figure 3.19: ASYS PK clinical trial - King's Hospital London.

The algorithm developed to synchronize the four protocol communications was more complex considering the sample times and baud rates of each device/monitor. The solution was to implement an algorithm in which different devices were given differents weight and priorities. The infusion pump data drug concentrations, infusion rates and volume infused had priority over the bispectral index, for example. However, the whole data was captured, synchronized and recorded in a file every 5s. The file was saved with the subject individual data. Communication from this version, figure 3.20, was proceed at clinical environment, it did not present any errors being validated to be used with subjects.

Based on ASYSPK another version was designed, the ASYS Simulation, as

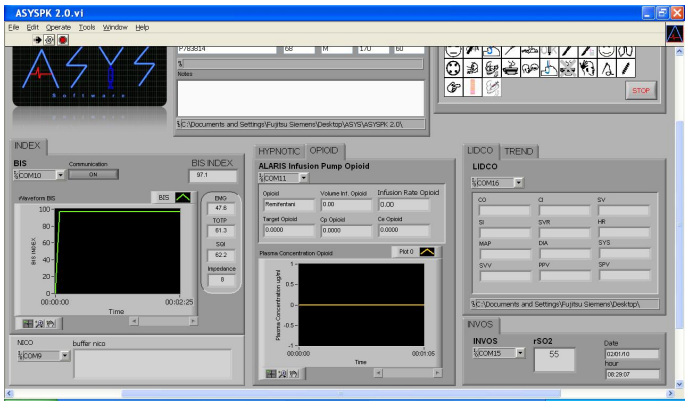

Figure 3.20: ASYS PK at King's Hospital London.

shown in figure 3.21. The ASYS Simulation was a version that simulates the PK/PD models for the hypnotic and/or opioid without hardware connections. ASYS simulation was developed with the novel IRCA as described previously. This version allows the physician or engineer to better understand how a TCI system works, how the pharmacokinetic parameters influence the TTPE; the infusion rates related to anesthesia phases (induction, maintenance and emergence), the influence of LBM or IBW on the PK parameters, etc. The pharmacokinetic/pharmacodynamic data was recorded every 5s in a Excel file together with the simulation subject data.

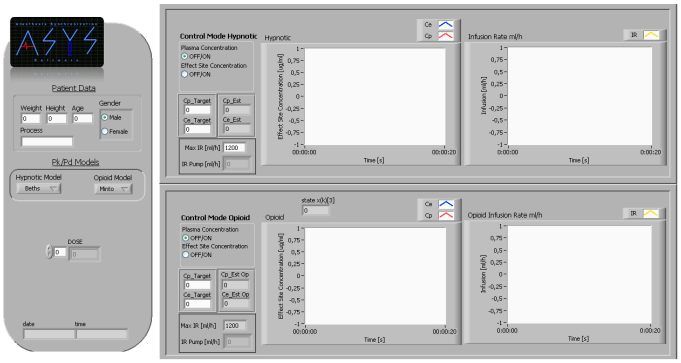

Figure 3.21: ASYS simulation screen.

The simulation version led the first version of ASYS with controlled pumps tested in clinical trial, as figure 3.22.

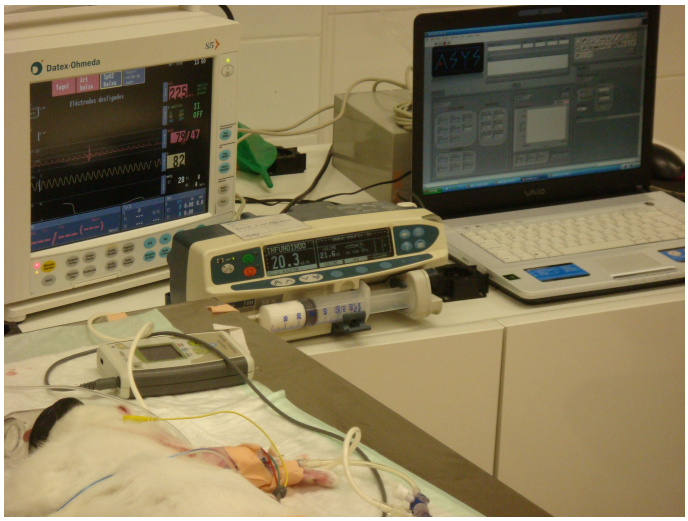

Figure 3.22: ASYS with controlled pump in clinical trial with rabits - UTAD.

Hospital Geral de Santo António

The final version of ASYS as a TCI system, was implemented with 5 different drivers: DATEX modular monitor, BIS cerebral monitor, ASENA infusion pump, LIDCO cardiac output monitor and the INVOS cerebral oximeter, as shown in figure 3.23. Two other options for cerebral monitors were also implemented: the Auditory Evoke Potentials and the IoC (Index of Consciousness) by Aircraft Medical.

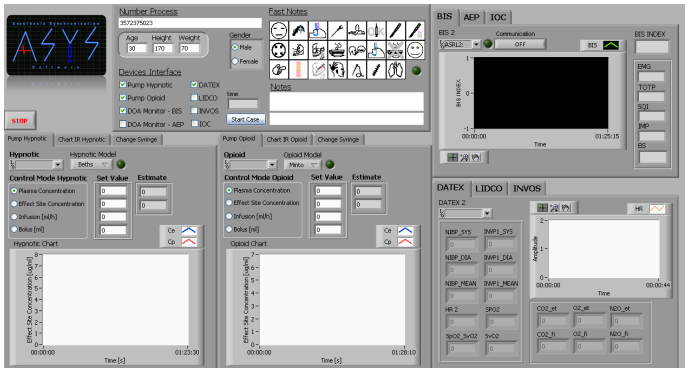

Figure 3.23: ASYS final version.

The protocol communication algorithm with 8 monitors/devices is complex and computationally demanding in itself. The algorithm was designed based on weights, priority and interruption request strategy (IRQ). The interruption is a software action used any asynchronous event arising from hardware, software or by the user action. The communication protocol algorithm was tested in the laboratory and did not present

errors as: data lost, corrupted data, time-delay data transfer or communications fail. This version records hardware alarm and logs in a text file with subject individual data, date and time.

The IRCA of ASYS full version has the novel controller implemented. ASYS was fully tested in the laboratory and in the clinical environment, as figure 3.24. The tests and results are presented in chapter 5.

The final and full version of ASYS, as shown in figure 3.24 includes:

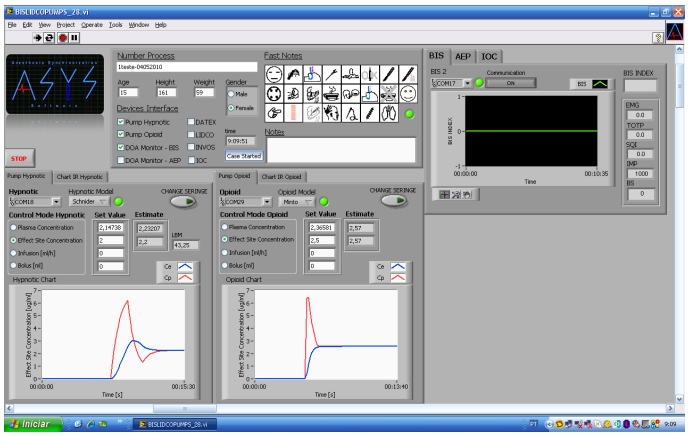

Figure 3.24: ASYS final version at Hospital Geral de Santo Antonio.

- Supervising and Monitoring: records the anesthesia data in real time changing set points, display graphical and alphanumeric representation on a friendly interface, choosing the serial port for communication, controlling pumps and drug doses. Stores data from all devices and user inputs in a file with alarms and historic data;

- Alarm: alarm for exceptional events that may occur during the procedure, with graphical signal or/and dialogue boxes so as to warn the anesthesiologist about their relevancy. The hardware alarms are related with the functions of infusion pumps and monitors during the procedure and recorded with date and time in a text file with the subject personal data.

  The alarm capture allows its analysis after the procedure, aiming at currently, improving or reseting a device/monitor program. Infusion pumpss alarms like:

end of drug, occlusion, excessive pressure, end of transmission, etc automatically stop the infusion suspending the IRCA until the alarm is cleared. On the drug adjustment settings the PK/PD model continues the estimation, showing the decrease in the drugs once the alarm is disabled the IRCA restarts considering the estimated concentration in the moment and the previous target.

- Control: ability to incorporate mathematical algorithms and pharmacological models, in order to evaluate adequate drug doses and anesthesia level. These should consider hemodynamic signals, brain signals or concentration limits matched with the anesthesiologist's judgment;

- Data Stored: the data provided by the 8 monitors/devices generates a file which is stored with the patients code;

- Report: during the medical procedure the user can write notes using the software interface window. These notes are recorded with date and time, so that they can be related with all stored data for posterior clinical analyses and discussion. These files are saved in a standard extension like ".doc" or ".xls" according to user option;

  The buttons at the top of the ASYS interface are called 'fast notes', each button representing a specific event, every time one these is pressed an automatic note is generated in the file. This option is simple and fast; and very practical specially if the anesthesiologist is busy attend to other tasks or if the physician is alone in the operating room controlling anesthesia and relating the important events of the procedure for future analysis.

- Data Base: a data base with patient's data (name either name or code, gender, age, height, weight, etc), anesthesiologist's data, surgery data and drug infusion data is generated for security reasons. This is required to prevent mistakes between patients or drugs.

Chapter 4

Intelligent Alarms

"So Einstein was wrong when he said, "God does not play dice." Consideration of black holes suggests, not only that God does play dice, but that he sometimes confuses us by throwing them where they can't be seen." - Stephen Hawking.

Introduction

Automation combined with control engineering and information technologies introduced new concepts and methods for human work in the production of goods and services. Automation is considered a step beyond mechanization replacing human work in monotonous and hard physical tasks; at dangerous environments; performing tasks beyond human capabilities of size, weight or speed and improving economically the companies, society and humanity.

Frei [77] published a study titled "Automation in Anesthesia", describing a fuzzy controller for inhalation anesthesia describing the modelling phase, implementation and clinical validation. In this study Frei described automation in the anesthesia procedure. The platform used for implementation was detailed and for the first time in anesthesia a software with *Supervisory Functions* was used. These functions included a Man Machine Interface (MMI), the physician directly interacts with it introducing by targets, monitoring variables and controlling the entire system. A Fault Detection and

Isolation function (FDI) is used to monitor and identify faults which can be model-based or signal processing based. Frei's implementation of a decision support system as an adviser tool for the physician to optimize the anesthesia procedure. Figure 4.1 from Frei's paper graphically represents the concept:

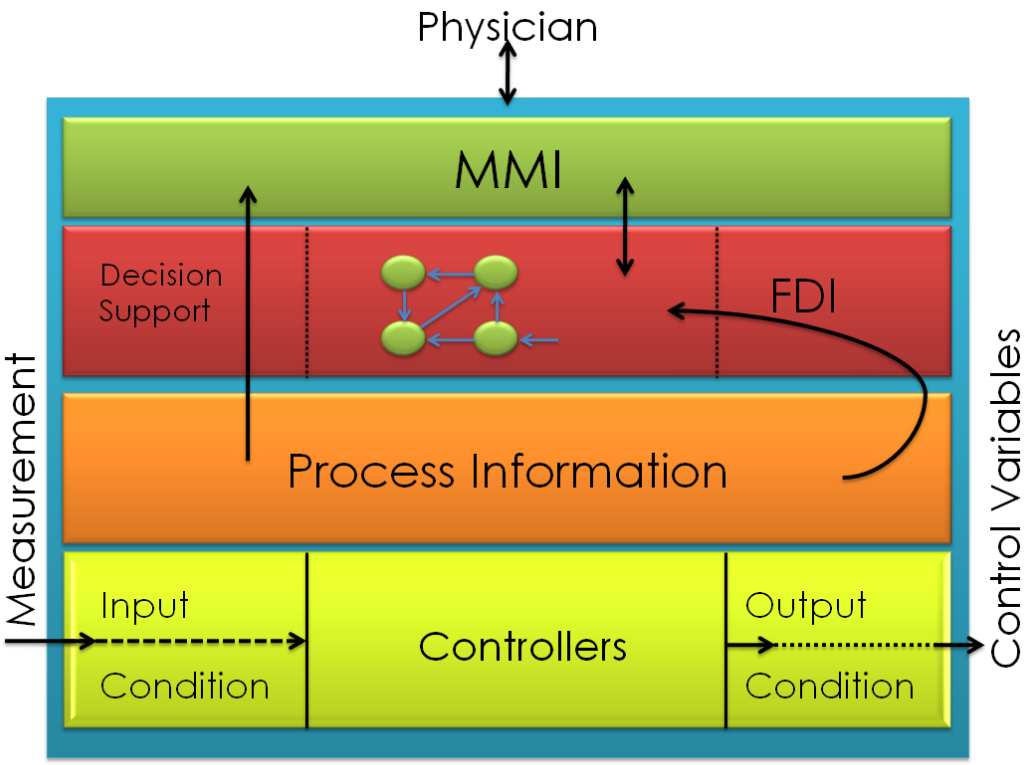

Figure 4.1: Supervisory Functions structure from Frei - Automation in Anesthesia.

Why automated Anesthesia monitoring?

To fill the goals of automation, it should replace human work when a task is monotonous and physically demanding; performed in dangerous environments or where a machine can perform beyond human capabilities.

The tasks performed by the physician during a case are of different kinds and quite demanding. First, there is the need to continuously monitor. This includes direct clinical assessment of the patient, assessment of physiological variables through the use of monitors and checking the function of medical devices used for anesthesia. This

needs to be done continuously and repeatedly over several ours. It is both monotonous and demanding and represents a source of fatigue and stress.

Interpretation of information from all these sources, as well as making decisions based on such information and specificities of the procedure and the patient, demand a lot of risk from the anesthesiologist, so that his or her attention remain at same level for all variables at same time.

Knowing that the physician's attention can be diverted, monitors and machines are equipped with all types of alarms. Alarms can be for physiological parameters but also for equipment failure.

Alarms go off very frequently, quite often not because of a change in the physiological parameters being evaluated, but because of electrical noise, artifacts from measurement, etc. All these factors contribute to generate a large amount of information to be processed by the physician. This can be easy beyond human capabilities. More than the amount information, false alarms and different levels of expertise of the physician must be considered in the right judgement during anesthesia [78]. Considering that monitoring patient data is a relevant step to assure the fourth component of anesthesia homeostasis, the automation for data monitoring is needed.

The current chapter presents the development of intelligent alarms as an integral part of the SCADA concept of ASYS. The goal of the inclusion of intelligent alarms in a TCI software was to bring automation in a literal way and improve the TCI technique with an advisory tool for the physician replicating a concept already introduced in anesthesia machines or workstations.

4.1 Alarms and Anesthesia

When the development of anesthesia software started in the earlies 1980's [56], modelling of drug behaviour and control of the model were the main concerns and receiving frequent improvements, Alvis [22] was the first to verify that device inaccuracy could influence the controller performance. White [37] presented not only an IRCA but, routines to control the infusion pumps and monitor alarm messages. Gray [79] in 1998 develop a Dirpifusor system and pointed out that such system must detect any failure or fault by: the microprocessor arithmetic logic unit, program memory failure, data memory failure or algorithm failure.

It became evident that monitors worked a very large amount of information, as showed in figure 4.2, and this information presented coming from the monitors and devices, with alarms and the clinical environment noise.

Kenneth was a pioneer of the intelligent alarms in anesthesia, presenting an artificial neural network (NN) for multivariable monitoring and pattern recognition to detect incidents and reduce false alarms; this study demonstrated with a simple approach, a method that can be used easily to update and incorporated an information system [80] .

Lowe proposed a different method using artificial intelligence (AI) and fuzzy logic to identify characteristic patterns in multiple time-series employing temporal pattern recognition based on linguistic rules [78]. The author also described [81] methods to highlight patient data in a way that reflects the fuzzy output algorithm applied. Lowe's study demonstrated that colourful alarms keep the physician attention to important features in the physiological variables implying detection of significant changes in clinical signal. Diagnostic is also improved by this 'intelligent monitor'.

Recently, Dunsmuir [82] developed a knowledge authoring tool (IKNOW) for

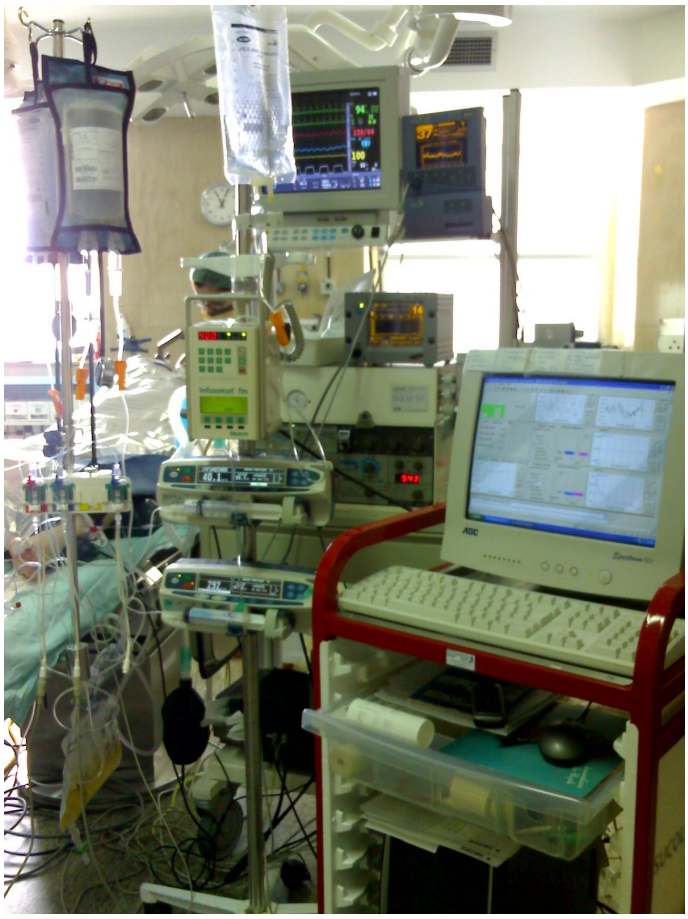

Figure 4.2: Clinical environment with monitors and devices at operating room.

physiological monitoring, where the physician creates its own rules to assess physiological data, to be warned and advised in case of incidents, alarms or false alarms. The rules were coded in the rule-based programming language C Language Integrated Production (CLPS) and manipulated through the Jess rule engine. The software IKONW is simple allowing complex chains of knowledge to be encapsulate, improving clinical care and reducing severe adverse events.

The concepts described above and the evolution of alarms in anesthesia, led to the decision of the implementation of a software with TCI technique, supervisory functions and incorporating intelligent alarms, ASYS [69].

4.2 Intelligent Alarms

Why Neural Networks?

The goal of intelligent alarms in ASYS is to be able to relate physiological data with pharmacokinetic and pharmacodynamic information during the anesthesia procedure.

From what can be considered as an initial phase of development, the physiological variables considered were: Heart Rate (HR), Arterial Pressure (AP), BIS, End-tidal Carbon Dioxide ($ETCO_2$) and Saturation of Oxygen (SpO_2); PK/PD data considering the estimated Ce for the hypnotic and the opioid. Considering the complexity and non-linearity of the data, neural networks technique were considered appropriate to pattern recognition to learn from input-output relationships and use sequential training procedures adapting itselves to the data [12].

The intelligent alarms of ASYS were developed using the programming language Matlab and its Neural Network toolbox. An algorithm developed in Matlab is presented in this chapter. In the future, an improved algorithm will be programmed in LabView and implement in ASYS.

The neural networks can be grouped in four categories of application:

1. Clustering: this algorithm explores the similarity between patterns and places similar patterns in a cluster.

2. Classification Pattern Recognition: the task of pattern recognition is to assign an input pattern to one of many classes.

3. Function Approximation: the task of function approximation is to find an estimate of the unknown function f subject to noise.

4. Prediction Dynamical Systems: the task is to forecast some future values of a time-sequence of data. Prediction differs from Function Approximation by considering time factor.

In this study the category Pattern Recognition was choosen as a supervised learning application, where a set of example pairs $(x, y), x \in X, y \in Y$ aims to find $f : X \rightarrow Y$ in the allowed class of functions that matches the examples. Figure 4.3 represents graphically how a recognition system works 'learning' with data and 'testing' (classification) data.

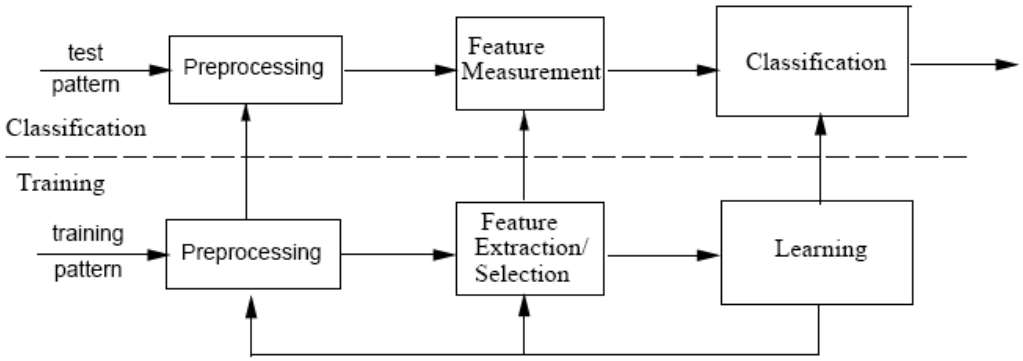

Figure 4.3: Model for statistical pattern recognition for Jain study. [12]

Aiming to optimize the development of the neural network to generate the intelligent alarms and considering the pattern recognition as a category, a radial bias function (RBF) was selected to implement the NN. A RBF is a network approach by viewing the design as a curve-fitting problem in a high dimensional space. Learning is equivalent to finding a mutlidimensional function that provides a best fit to the training data, with the criterion for best fit being measured in some statistical sense [83].

The NN structure is composed by two layers: a hidden radial basis S^1 neurons and an output linear layer of S^2 neurons, represented in figure 4.4:

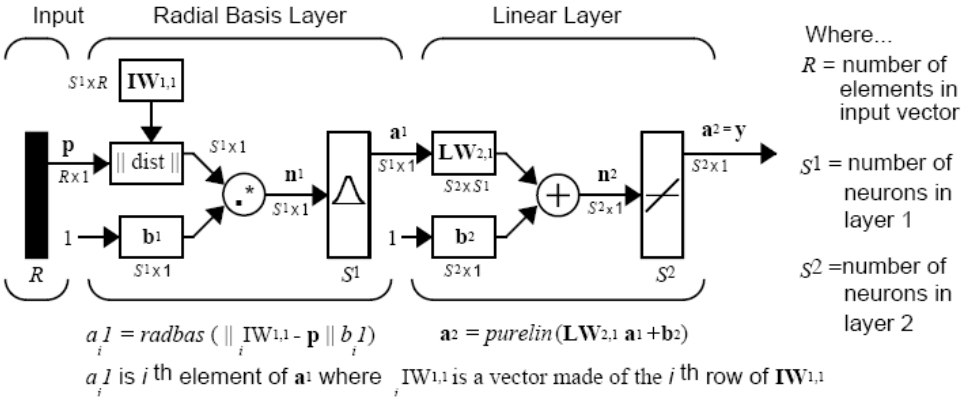

Figure 4.4: Network Architecture from Matlab ToolBox Manual.

4.2.1 Implementation

The implementation of the intelligent alarms followed three steps:

1. Data Collection:

   Patient data, used to train and test the neural network, was collected during neurosurgery procedures at Hospital Geral de Santo António, two days per week, during 3 years of the present research. Data were collected in cases performed using general anaesthesia, every 5s using Rugloop with TCI. Anesthesia was performed with remifentanil (Remi), propofol and one of two muscle relaxants: rocuronium and vecuronium used according to the physician criteria.

   Collected data were recorded in Excel files with: patient code, ASA, weight, height, age, LBM, gender, HR, AP, BIS, CO_2 and SpO_2. Patients without major diseases (ASA 1 and 2) were considered for algorithm implementation and testing.

2. Data Rules:

   Studies relating TCI technique with the hemodynamics were performed during the evolution of TCI systems [84]. The administration of the anesthetic drugs during general anesthesia was intensively studied, relating the titration with the variability of HR, cardiac output and mean arterial pressure [54], [85].

Considering the evidence relating these physiological variables and TCI technique the first two variables to be implemented in the intelligent alarms were the heart rate and the arterial pressure. Possible combinations of high, low, normal status for HR and AP are showed in the following table:

Variable	Status	Variable	Status	Alarm Code
HR	high	AP	normal	1
HR	low	AP	normal	2
HR	high	AP	high	3
HR	high	AP	low	4
HR	low	AP	high	5
HR	low	AP	low	6
HR	normal	AP	high	7
HR	normal	AP	low	8
HR	normal	AP	normal	9

Where:

Value of HR:

- high above 100
- low below 40

Value of AP:

- high systolic blood pressure above 140
- low systolic blood pressure below 90
- high diastolic blood pressure above 90
- low diastolic blood pressure below 60

3. Application of the design function RBF by Matlab:

   Considering the data rules and using the function RBF from the Matlab toolbox, an algorithm was implemented to develop the neural network.Matlab builds the NN using the following inputs: P and T.

   The matrix P is the input with HR and AP; the vector target 'T' the alarm code and a mean squared error goal equal to zero. The function returns a network with weights and biases with the outputs for T when the inputs are P. In this first implementation of NN, the variables: BIS, CO_2, SpO_2 and effect-site concentration of propofol and remifentanil were not considered, since an detailed analysis is need to establish their relation with HR and AP.

To train the NN several patients were used, however the outliers (e.g. different anesthesia protocols, errors in the insertion of patient data, etc) result in impossibility to use of patients data. A random patient was choosen to train the NN with 500 data points, and the remaining 300 points were used as validation set. The data was from an patient at different phases of the surgery. The points used to train included alarms code 1 and 8. The test group verified the alarm code 8 without failure for all points tested. The performance of the NN presents zero error between P and the output for random patient data. The validation test in this patient resulted in 100% match with the alarm code from the training set; without false negatives or positives.

The development of the neural network for intelligent alarms to be used in ASYS demonstrated to be simple and viable. The use of the neural network establish a path to follow in the future implementation of all variables into the intelligent alarms. However, lack of time did not make it implementation possible in LabView language for clinical trials and validation. The implementation of all intelligent alarms in ASYS to finally compose de totality of the SCADA concept is part of the future work addressed

in chapter 6.

Chapter 5

Results

Our deepest fear is not that we are inadequate. Our deepest fear is that we are powerful beyond measure... - Marianne Williamson

Introduction

The design and implementation of a project for the generation of new knowledge of its application, is one of the goals of this work. This chapter presents the hypothesis tested during the software implementation, the results of the methods and techniques applied to develop the IRCA, the results of laboratory tests and the test of ASYS in the O.R. connected to devices/monitor but without patient.

The design and implementation of a SCADA for anesthesia was described along 4 chapters to accomplish the proposed goal. The Data Acquisition component of the Anesthesia SCADA was presented at chapter 2. This chapter demonstrates the evaluation of the communication system and interaction of all devices/monitors already published, as well as the communication protocol improvements in ASYS.

The Supervisory and Control components of the SCADA were described in chapter 3 and 4. The Control component was the most meticulous and detail part of the system to be develop, implement and test.

In the current chapter, the expression 'results' is used when referring to publications where the first author is the author of this thesis. This 7 publications were included in the references list at the end of this thesis. The results are presented in the chronology order of the publications, which follows the natural path of development of the full SCADA. This chapter shows the contribution to TCI and Automation in Anesthesia.

5.1 Results I - Plasma Concentration Control

The first results with ASYS were obtained in communication tests. The tests of the communication protocols were done staged; first in separated programs and then in an algorithm with all monitors and devices. The first publication addressed the communication with two monitors, one infusion device and the Marsh model [19] as a controlled PK model [86].

This work presents a computer aid for anesthesia incorporating a modular monitor. This provided more information to evaluate the adequacy of anesthesia through out the surgical procedures. Data from Datex combined with consciousness indices gather information for the physician interacts with ASYS adjusting the desired drug targets.

Datex is a essential tool to evaluate homeostasis, physiological variables as heart rate, blood pressure or plethysmography that can be used to assure adequacy of analgesia and hypnosis. Physiological variables: heart rate, blood pressure, oxygen saturation, Spo_2 for example, combined with pharmacokinetic data are interpreted and allows the physician to adequate anesthesia. The device used was a DATEX©Ohmeda S/5 by *General Electric (GE)*. The communication between ASYS and the modular

monitor was described at chapter 2.

This version of ASYS used Alaris Asena GH by Alaris®Medical Systems, as the infusion device, and BIS by Aspect (later Covidian) as a cerebral monitor. The study was divided in two phases: a phase of communication protocol development and testing and a second phase testing the implementation of a propofol model and controller.

The communication protocol for DATEX©was described at chapter 2 composed by standard parameters as: start bit, stop bit, baud rate, and including security routines like: particular characters on the data frame indicating an exact variable; a start code and checksums for each group of bytes. The protocol was developed in LabView as a separated routine, tested and added to the main software algorithm.

This first version of ASYS used with Marsh model for propofol with differential equations for three compartmental model to estimate plasma concentration. The IRCA implemented control the plasma concentration was a BET scheme, guided by Alvis's rules [57]. Two simple tests were done to evaluate ASYS performance:

1. Bolus Test: 10ml were administered considering a 70kg subject.
2. Plasma Concentration Mode: two targets of 1% propofol were set: first $C_p = 3ug/ml$ until the maintenance phase then $C_p = 5ug/ml$ kept until steady state.

The BET scheme was the first option for a controller to be implemented in ASYS. However, the results presented errors in the drug dose administrated. The study showed that the error from the infusion device or the real time interaction were not taken into account in the IRCA. This important part of the controller should not have been disregarded. This finding was the start of the research on TCI controllers and their optimization. This research revealed that must of the existent TCI systems

adopted Bailey's plasma controller avoiding the errors that we found.

When the research that led to our initial publication was planned the main idea was a modern version of Alvis's system [57]. Interestingly we later found out that Alvis, in a subsequent study, identified and corrected errors originated from the controller and the pump which were exactly the same that we encountered.

Jacobs [63] presented a solution to this problem considering error from the infusion device; his solution was the one that was later implemented in ASYS. The IRCA compares the real infused volume with the C_p and calculates the correct infusion rate to achieve C_{pT} set. The second publication in the development of ASYS was a studyto implement a solution for this problem [87].

In this study ASYS was compared with a commercial TCI system. Base PrimeaTM (Fresenius, France) was the commercial device used. It uses a microprocessor while ASYS remote control the infusion device Asena GH MK III pump (Cardinal Health, Alaris Products, Basingstoke, UK).

Several tests with different subjects and propofol protocol were performed. The data from ASYS was collected every 5s and data from Base Primea was recorded manually. Assuming that the pumps would be infusing propofol, predicted drug plasma concentrations were calculated by both systems using Marshs Pk model with $k_{e0} = 0.26min^{-1}$.

Bench tests were performed a beaker was used to collect the infused fluid amount. The test aimed at establishing a relation between the two systems and understand how the IRCA implemented in both systems worked with the infusion device feedback. For each test, an infusion rate and duration were set and the fluid infused was collected on a beaker. At the end of the test, the infused volume displayed by

system was recorded and the beaker was weighed. A high performance scale, Kern PLS4000-2 (by DSW) was used.

The performance error (PE) of ASYS, between displayed and measured volumes was $2,55 \pm 3,45\%$. The PE between the displayed and measured volumes on Base Primea was $3,65 \pm 5,5\%$, both shown in figure 5.1.

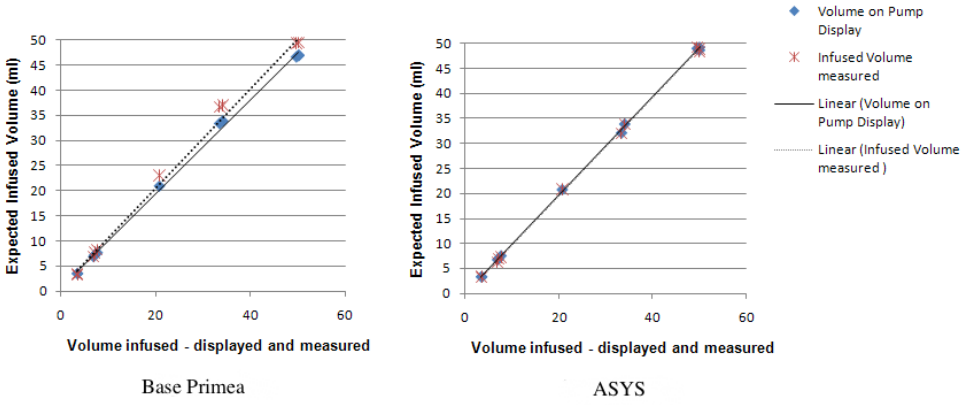

Figure 5.1: Expect infused volume [rate/time] vs the volume infused displayed on the systems. A linear trend is also showed.

The results presented in this study demonstrated that ASYS performed similar to Base Primea with infused amounts average error of 2.6%. These was the first evidence that ASYS could be a reliably tool to drive an infusion pump in a clinical environment.

However, several different algorithms can be used, as addressed in previous chapters to control plasma concentration. A study published in 2004 by Ting [67] described an equation for maintenance considering the three initial volumes of the PK model. The equation for maintenance infusion presents a first term as bolus to fill the central compartment, a second term for the elimination to the central compartment and the third one represents redistribution to peripheral compartments, describing a

BET scheme.

Ting's equation 3.11 called our attention to the probability of improving the IRCA of ASYS which used Alvis's rules and equation 3.8. This question was addressed in the third publication [88] which analysed Ting's and Alvis's methods to try to find the most efficient method for the maintenance phase in an open-loop control TCI system. The goal was the improvement of the existing ASYS software with a new method for the maintenance phase.

An Asena GH MKIII pump was assessed and remotely controlled by ASYS. The drug used was propofol and the pharmacokinetic model used was Marsh [19].

Two different versions of ASYS were developed and tested to evaluate their performance, as follows:

- ASYS Version 1:

  This version was implemented with Alvis equations and device rules for continuous infusion, integrated with Jacobs [26] concept to predicted and control C_{pT}. The two equations by Alvis combined, represent the initial drug dose to reach the target concentration, and the maintenance equation to keep the set target. A controller similar to Jacobs's [63] was added to this algorithm, where every 10s a feedback from the syringe pump gave information to the algorithm about the real volume and related with the C_p estimated. The subsequent plasma concentrations and infusion rates are calculated based in this feedback.

- ASYS Version 2:

  This version of ASYS implemented Ting's equation [67], where at $t = 0$ a bolus or initial drug dose is administered to reach the target and at $t \neq 0$ the maintenance is set to keep the target. To this algorithm a similar plasma controller of Jacobs [63] was added following what was described in the First Version.

The tests performed with both versions aimed at evaluating accuracy and efficiency. A $70kg$ male patient was considered in both versions of ASYS for simulation. The protocol used was as follows: initial propofol plasma concentration target was set at 3ug/ml and kept until steady state was reached; the target was then changed to 5ug/ml and kept until steady state was reached.

These results showed version 2 was more efficient than version 1 in both tests. Version 1 presented a lower bolus than version 2; also, version 1 was slower than version 2 to reach $C_{pT} = 3ug/ml$, as figure 5.2. Version 1 also showed a delay in the time to reach the target, presented when compared to version 1.

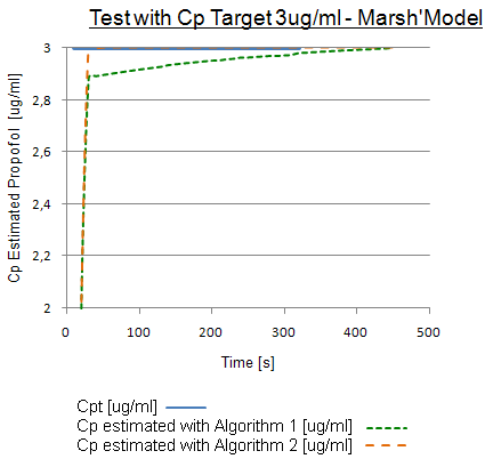

Figure 5.2: Results from Version 1 and 2 with $C_{pT} = 3ug/ml$.

The different system behaviour presented by these two versions could be justified by the different initial drug dose administered. Version 2 was considered more efficient during maintenance, performing similar to commercial systems for TCI.

Once could be tempted to assure that the implementation of Ting equations would result in a ideal IRCA, however our research led us to believe that a better solution for the controller could be found. This revealed in part from our analysis of existing algorithms of Poucke [66] and Shafer [17]. In fact a novel controller could be developed, addressed in detail in chapter 3. It started with a controller for plasma

concentration followed by a controller for effect-site. A fourth study, published in 2010 [89] presented the method used to develop the controller and the first results of its implementation.

The controller implemented uses an analytical solution which uses a matrix based control rule, discrete in time with a state space model in order to the input drug dose I. The same method was later applied to control C_e. The results demonstrated a simpler mathematical algorithm with accurate performance to be used at clinical environment. Figure 5.3, shown the similarity of ASYS using the novel controller and Rugloop using the traditional TCI controller.

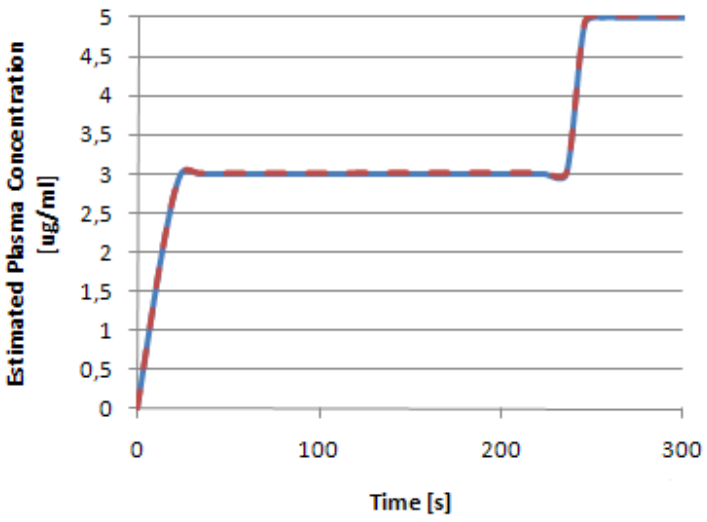

Figure 5.3: Estimated Plasma Concentration at Rugloop I and ASYS.

5.2 Results II - Effect Site Concentration Control

The next step in the ASYS development was the effect-site concentration control which demand a intensive computational approach[63] but represents an efficient control of anesthesia allowing physicians to estimate the concentration in the site of control. The

controller developed in the study in 2010 [89] was the base for the development for the effect-site concentration controller using the same mathematical method.

The study [68] presented a novel controller for plasma and effect-site concentration, to be used in TCI systems using optimal control technique. The novel controller demonstrated a good response in steady state, figure 5.4. Aiming to eliminate the overshoot identified in some controllers, the optimal control technique was implemented in the novel controller, as described in chapter 3.

The results with the novel controller provide enough arguments of a robust and a reliable IRCA. This study presented an algorithm mathematically simpler than most of the existing algorithms and the results shown that it performance accurately.The fact it is simpler may offer advantages when used in the clinical set up to control infusion devices. Clinical trial tests will be needed to fully assess it performance. In future work the optimal control will be tune with Lean Body Mass (LBM) and the target of effect-site.

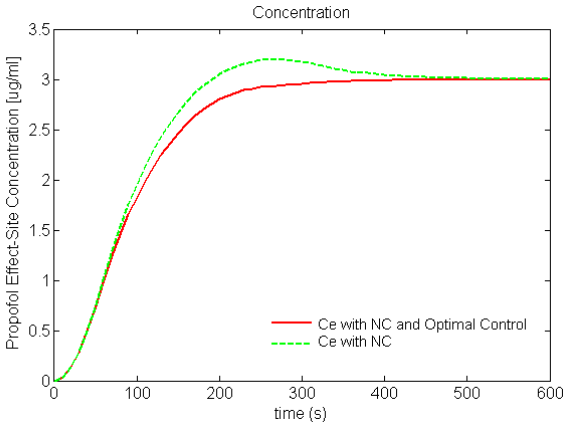

Figure 5.4: $C_e = 3ug/ml$ of propofol with the novel controller and without the optimal control.

5.3 Results III - System Evaluation

The sixth study published in 2010 [90] presented a set of tests to validate the performance of a TCI system as a computer-aid. The study assessed the performance of ASYS, on a clinical setting to evaluate communications consistence (computer - infusion device) and controller performance in real time. The tests measures provided quantitative and qualitative evidences of software robustness (infusion pump's error) and accuracy to be used in a clinical environment.

The main function of a TCI system is to reach and maintain a stable concentration, defined by the physician (the target). According to Varvel [91], the good performance of a TCI system can be measured from the error between C_T and the estimated concentration. The smaller the error the greater the accuracy of the TCI system. In this study reliability, consistency and accuracy of ASYS control algorithm and communication consistence, between computer and the infusion device, were evaluated in real time.

In order to be used in the clinical environment, a TCI system needs to satisfy restrict and specific conditions in operation [23], [91]. According to Engbers [92] TCI systems (Diprifusor) could present some errors related with this technology like: dead space, infusion device malfunction or computer performance. Our study evaluated the performance of ASYS with the novel controller implemented. The tests showed the performance of the system as a software considering the PK/PD model, the IRCA and the communication with several devices simultaneously.

ASYS was tested with the three compartmental model by Marsh modified for propofol ($k_{e0} = 0,26min^{-1}$), and 70kg male subject was considered. The tests were performed with ASYS in real mode. The infusion device used was the syringe pump Alaris Asena GH. During the simulations another syringe pump was connected simulating analgesic infusion. A cerebral monitor, BIS XP was also connected to collect

the signal for DOA. The syringes used were empty and the data synchronized every 5s.

The set of tests performed were partially defined by Shafer [23] as follow:

1. Maintain a steady state propofol C_p and C_e for three clinically useful concentrations: 2, 5 and 10 ug/ml. Each C_T was kept for 1h.

2. Increase the C_{pT} and C_{eT} from 5ug/ml to 10ug/ml. Each C_T was kept for 1h.

3. Decrease the C_{pT} and C_{eT} from 10ug/ml to 5ug/ml. Each C_T was kept for 1h.

4. Insert a malfunction into the pump during 10min. Evaluate the ability of ASYS to keep the C_{pT} and C_{eT} at target of 10ug/ml.

5. Maintain a steady state propofol C_p and C_e for three clinically useful concentrations: 1, 1,5 and 2 ug/ml. Each C_T was kept for 1h

To measure the error between estimated concentration C_e and C_T were used Percentage Performance Error (PE) was used as follows:

$$PE_{ij} = \frac{C_{eij} - C_{Tij}}{C_{Tij}} \cdot 100 \tag{5.1}$$

The results presented no relevant error between C_e and C_T, as follows:

1. Maintain a steady state propofol C_p and C_e for three clinically useful concentrations: 2, 5 and 10 ug/ml. The target concentration for C_p of 2, 5 and 10ug/ml presented no error during 3h in total. The target concentration for C_e=2ug/ml presented an overshoot of 4%; C_e=5ug/ml an overshoot of 0,6% and C_e=10ug/ml an overshoot of 0,7%.

2. Increase the C_{pT} and C_{eT} from 5ug/ml to 10ug/ml. The increment from C_{pT}=5ug/ml to C_{pT}=10ug/ml resulted no error during 1h. The increment from C_{eT}=5ug/ml to C_{eT}=10ug/ml resulted in 0,5% of overshoot during 1h.

3. Decrease the C_{pT} and C_{eT} from 10ug/ml to 5ug/ml. The decrement from C_{pT}=10ug/ml to C_{pT}=5ug/ml resulted no error during 1h. The decrement from C_{eT}=10ug/ml to C_{eT}=5ug/ml presented an overshoot of 0,2% during 1h.

4. Insert a malfunction into the pump during 10min. Evaluate the ability of ASYS to keep the C_{pT} and C_{eT} at target of 10ug/ml. The C_{pT} presented no error after the pump failure. The C_{eT} presented an overshoot of 0,2% of C_{eT}=10ug/ml after the pump failure.

5. Maintain a steady state propofol C_p and C_e for three clinically useful concentrations: 1, 1,5 and 2 ug/ml. The C_{pT}=1ug/ml presented an overshoot of 2%; C_{pT}=1,5ug/ml an overshoot of 2% and C_{pT}=2ug/ml an overshoot of 2% during 3h. The C_{eT}=1ug/ml presented an overshoot of 1%; C_{eT}=1,5ug/ml an overshoot of 0,7% and C_{eT} =2ug/ml an overshoot of 2% during 3h.

Results of the set of tests applied to ASYS are encouraging regarding its use in a clinical environment. The software confirmed reability, consistency, accuracy and robustness while communicating and controlling three devices at same time without loss of data or failure occurrence. The test also demonstrated a good performance of the novel controller in real time, reaching and maintaining the target concentration. ASYS demonstrated to be a reliable tool as a computer-aided for anesthesia.

Chapter 6

Conclusions

Embora ninguém possa voltar atrás e fazer um novo começo, qualquer um pode começar agora e fazer um novo fim. - Francisco de Paula Candido Xavier.

6.1 Main achievements

This thesis described the development of a SCADA (supervisory, control and data acquisition) system for clinical use in general anesthesia. It's development, implementation and validation tests were presented throughout the previous five chapters. To the best of the author's knowledge, ASYS is the first SCADA for anesthesia that incorporates a TCI system.

This thesis discussed the relevance of automation in anesthesia, where monotonous tasks, physically demanding or beyond human capabilities were successfully replaced by automation. Solutions were presented to automate alarms, to control drug administration and to acquire data. Each topic was addressed starting from the conception through the implementation process and ending in the final system.

The thesis also described driver implementation for several different devices and monitors. Chapter 5 summarized the main results based on work published along the PhD. The main achievements of each chapter are summarized here together with

a suggestion for future work.

6.1.1 Communication Driver

Main achievements

The communication driver chapter described the implementation of the protocol communication provided by the manufactures for medical equipment. At first examination, not only for laypeople but also for engineers, this task looks like a easy one. However the specificity, details and the intrinsic safety issues related to clinical use, elevate the difficulties of this task of driver implementation and development.

The implementation of the communication protocols was the basis for the development of data acquisition of the SCADA. Beyond driver implementation, all data, like error, alarm, or information from the equipment must be captured, treated, classified as hardware, software or user error in order to be recorded for posterior analysis. The final algorithm of ASYS with 8 different drivers working at the same time, represented a relevant achievement. Considering that ASYS is also control and supervise system, beyond data acquisition and synchronization.

Future work using ASYS as a SCADA should be the development of an ASYS application for remote use with the concept of Remote Terminal Unit (RTU) with network or distributed architectures. The remote ASYS could be updated via internet allowing the use of TCI around the world, to capture data from specific surgical procedures of relevance to the scientific community or simply wireless data acquisition between induction room and operating room.

6.1.2 Target Controlled Infusion

Main achievements

The implementation of TCI technique in the Anesthesia Synchronization Software was more than testing of algorithms and known methods for drug delivery in anesthesia, it represented the development of a novel controller for plasma and effect-site concentration.

This novel controller is numerically simpler than the existing TCI controllers, computationally undemanding, reaching and maintaining the target concentration without overshoot following the BET scheme. The simplification of systems into one equation to administer a drug dose improved the accuracy and decreased the error related with numerical manipulation. The controller is promising tool to be used in TCI systems, however it still requires testing in the clinical setting.

Another achievement was the flexibility of the system. ASYS is completely configurable through the insertion of different PK/PD models, different controllers and different devices for data acquisition. This flexibility, with adequate constrains and limits, became a powerful tool allowing the physician a wider range of devices when administering general anesthesia.

6.1.3 Intelligent Alarms

Main achievements

Intelligent alarms were developed over the last decades and implemented in advisory tools to assist physicians, also improving the diagnosis of critical situations prior to their occurrence and are another powerful tool in anesthesia. The diversity in the design and implementation of intelligent alarms increased in the last years.

The development of intelligent alarms in ASYS had the main goal of supervisory tool automating the task heretofore accomplished by the physician. The simplicity of their implementation with neural networks, keeps the system open allowing the insertion of new alarms and controllers. The main achievement here was creating a TCI system that is also a supervisory system warning the physician for excessive concentrations or critical situations prior their occurrence, a feature not available in existing commercial or research TCI systems.

Improvements in the relation between TCI systems and intelligent alarms will allow the development of a closed loop control system for anesthesia. Considering, that there are no consensus in which is the best variable to assess hypnoses and analgesia, perhaps the right answer will be a combination of variables to establish depth of anesthesia or analgesia-nociception balance. Intelligent alarms as a feedback system integrated in a closed-loop controller will be the next challenging step in the improvement of the Anesthesia Synchronization Software.

Measure not the work until the day's out and the labour done. - Elizabeth Barrett Browning

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