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Target Controlled Infusion Algorithms for Anesthesia: Theory vs Practical Implementation

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Abstract— **Target Controlled Infusion (TCI) systems are based in drug pharmacokinetic and pharmacodynamic models implemented in an algorithm to drive an infusion pump. Infusion control algorithms have been designed, implemented and validated for several anesthetic drugs, devices and controllers. The maintenance phase in these algorithms is represented by an equation that compensates the loss of drug from the central compartment and maintains the set target concentration. The goal of the current study was to improve existing TCI software with a new method for the maintenance phase. We compared and analyzed two different methods to find the more efficient method for the maintenance phase in an open-loop control TCI system.**

I. INTRODUCTION

General anesthesia is defined by three main components: unconsciousness, analgesia and lack of motion; the drugs used to maintain these components are the hypnotics, analgesics and muscle relaxants, respectively. When the anesthesiologist administers a drug to a patient, he/she expects a specific effect on the patient, and the problem resides on knowing the precise amount of drug that is necessary to produce that effect on the particular patient. To answer this typical question one must understand how the drug is processed in the body.

The interaction between a drug and the organism is divided in two phases: pharmacokinetics and pharmacodynamics. Pharmacokinetics is described as "what the body does to the drug" and pharmacodynamics as "what the drug does to the body" [1]. Pharmacokinetic and dynamic models were mathematically manipulated considering particular patients' characteristics resulting in specific parameters. These models predict plasma and effect-site concentrations.

Since the 60's medical researchers [2] have been developing mathematical models to describe the behavior of drugs in the human organism. The pharmacokinetic model found the software developed to control infusion devices leading to new techniques applied to anaesthesia delivery. Target Controlled Infusion (TCI) is a denomination adopted in 1997 [3] to define the computer-assisted infusion devices. These software were used for drug infusion in open loop control allowing the physician to set a target plasma concentration (Cpt) or target effect site concentration (Cet) to reached a specific effect.

TCI systems are used to drive infusion devices using control algorithms implemented and validated for several anesthetic drugs and types of controllers. Infusion control algorithms (IC) follow the infusion scheme called BET (Bolus, Elimination and Transfer)[4] where a bolus is given as a fast dose to fill the central compartment; and a continuous infusion is kept to replace the drug eliminated from the central compartment and transfer between the peripheral compartments [6]. Considering the BET concept, the structure of the IC algorithm was delineated in bolus and maintenance.

The goal of this study was to improve our existing software, Anaesthesia Synchronization Software (ASYS)[5], developed in LabVIEW 8.2 (National Instruments), by implementing two different methods to establish the more efficient maintenance algorithm, to keep plasma concentration at target. Section II introduces the concepts of Pharmacokinetic Models and TCI systems. Section III describes the IC developed and implemented over decades to control Cpt. The fourth section presents the material and methods used to develop the two versions of ASYS. The fifth section describes the implementation of two maintenance algorithms. Section VI analyzes the results of the comparison tests between the two algorithms followed by section VII showing the advantages and future developments.

II. PHARMACOKINETIC MODELS AND TCI SYSTEMS

A. Pharmacokinetic Models

The behavior of anesthetic drugs can be well described for two and three compartment models. This study used a three compartment model published by Bryan Marsh et al [7] to describe the anesthetic drug propofol. The pharmacokinetic three compartment model is represented in Fig.1. The drug administered to compartment $V1$ is transferred to the second and the to third compartment by rate constants represented for k_{ij}, where ij represents the transfer between i and j compartments.

The rate constant k_{10} represents the elimination constant through the organism elimination process. The rate constants were used to determine the infusion rate and the maintenance infusion to reach the Cpt. Considering $m1$, $m2$, $m3$ the drug amount into each respective compartment:

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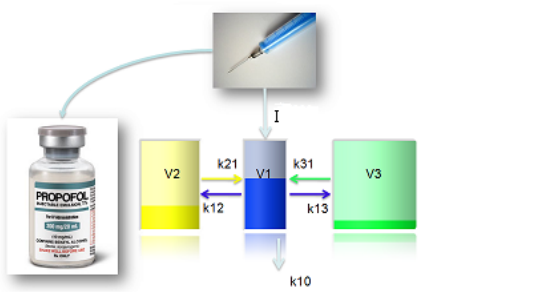

V1: central compartment, V2: second compartment, V3: third compartment
I : drug infusion [ml/h]

Fig. 1. Three-compartment model.

$$\frac{dm1\,(t)}{dt} = k21 \cdot m2\,(t) + k31 \cdot m3\,(t) - (k12 + k13 + k10) \cdot m1\,(t) + I\,(t) \quad (1)$$

$$\frac{dm2(t)}{dt} = k12 \cdot m1\,(t) - k21 \cdot m2\,(t) \quad (2)$$

$$\frac{dm3(t)}{dt} = k13 \cdot m1\,(t) - k31 \cdot m3\,(t) \quad (3)$$

where I is the infusion rate in ml/h.

TCI control in anesthesia could be described as an open-loop, once the drug dose is preprogrammed to achieve and maintain a desired plasma concentration. The plasma concentration is obtained as the concentration in central compartment. The estimation of plasma concentrations is based on model interaction, described in previous studies [7] for a certain population.

B. TCI Systems

The TCI concept [3] defines a computer-assisted infusion device that allows the physician to control theoretical plasma or effect site concentrations by setting a target for a specific desire anesthetic effect. Theoretically, TCI software should estimate concentrations at any body compartment [8].

In 1981 Schwilden [9] programmed the first microprocessor model 6502 to control an infusion device. The microprocessor controlled two syringe pumps: one with the analgesic drug and the other with hypnotic drug. In a study with 7 volunteers and 5 patients, he found the limitations to administer a bolus based in the mechanics of the pump as well as mechanic inertia on the pump operation around 15s. Since Schwilden's first experiment several researchers have developed, improved and optimized the control of drug concentrations in the body using TCI systems.

The advantages of TCI over manual anesthesia were cited recently by Xavier [10]. TCI systems can control each component of anaesthesia; they can be independently regulated and adapted to changes during different phases of a procedure. Coetzee [11] enumerated several benefits of TCI with BET: easiness to assess the relationship between drug concentration and effect; compensation for any interruption to the infusion; prediction of time to recovery and possibility of targeting the effect site. Moerman [12] claims that TCI algorithms were able to evaluate the complexity of drug pharmacokinetic characteristics better than manual administration method. TCI systems bring accuracy, velocity and reliability in the plasma and effect site control compared with manual anesthesia procedures [8].

III. INFUSION CONTROL ALGORITHMS

TCI systems are based in BET schemes that were improved by several researchers resulting in IC. In 1985, Alvis [13] developed the computer-assisted continuous infusion CACI, which is a tool that allows the physician to change the set point intraoperatively based on clinical judgment. CACI was tested in 20 patients under surgery, and its infusion control algorithm was based in a three compartment model, considering the differential equations 1, 2 and 3.

Considering the microprocessor of the pump used in his study, Alvis[13] encountered a problem when the pump accepted only integers numbers as the infusion rate. The solution was corrected the doses using the difference between the theoretical and the real dose. Every 15s a propotional control algorithm ($Totaldose$) compare the theoretical and the real dose from the pump adjusting the infusion.

$$Totaldose = LD \cdot (1 + k_{10} + \left(\frac{k_{12}}{k_{21}}\right) \cdot \left(1 - e^{-k_{21}t}\right) + \left(\frac{k_{13}}{k_{31}}\right) \cdot \left(1 - e^{-k_{31}t}\right)) \quad (5)$$

where:

$LD = Mp \cdot Cpt \cdot Vc$ (4)

Mp : patient weight

Vc : volume central compartment

To keep the plasma concentration constant, a continuous infusion must be kept. Following this concept Alvis [13] created a control routine. When a new plasma concentration target (NCpt) was set the algorithm follows three basic conditions to perform the control infusion:

1) $NCpt > Cpt$ (actual plasma concentration): When the physician increases the plasma concentration, a fast infusion is administered (bolus). The next equation, *additional loading dose (ADDLD)* is used to increase the drug amount [13].

$$ADDLD = (NCpt - Cpt) \cdot Vc \cdot Mp \quad (6)$$

$ADDLD$ aims to reach a level near $NCpt$, making possible to maintain a drug dose by a constant infusion compensating the distribution and elimination of the drug. After the plasma concentration increases from Cpt to $NCpt$, a constant infusion is maintained, calculated by the following equation [13]:

$$u(t) = NCpt \cdot Vc \cdot Mp \cdot \left(k_{10} + k_{12} \cdot e^{-k_{21} \cdot t} + k_{13} \cdot e^{-k_{31} \cdot t}\right) \quad (7)$$

2) $NCpt = Cpt$: When the plasma concentration was reached the maintenance infusion is kept, until the physician changes the target, or the control mode of infusion to a bolus or a specific infusion rate.

3) $NCpt < Cpt$: If the plasma concentration is decreased by the physician the software infusion algorithm stops until $Cpactual$ reached the target concentration. After reached the Cpt a maintenance infusion starts to keep the target.

The software CACI was tested several times and considered reliable for changing plasma concentration intraoperatively based on clinical judgment [13].

Jacobs [15] developed an algorithm to control the plasma concentration. After setting a target for Cpt an infusion rate starts to fill the central compartment to achieve the Cpt, a command is given to the syringe pump to administer the drug. In this period of infusion, the algorithm developed estimates the next plasma concentration ($Cpt\,(t + \Delta t)$) based on the first infusion and consequently calculates an infusion rate (I_1) to reach this $Cpt\,(t + \Delta t)$. This simulation was repeated estimating another Cpt_2 and a second I_2 related with it.

This two estimated points composed a polynomial line that is exploring the linearity of pharmacokinetics model and from this polynomial a point is used as an $Iideal$ infusion for the next Δt. This was repeated every 15s. This algorithm represents a control of plasma concentration during the IC demonstrating robust results for controlling central compartment concentration.

Ting [17] presents an equation for maintenance infusion following the BET scheme. The first term of the equation (8) is the initial bolus to fill the central compartment, the second term represents the elimination from the central compartment and the third one represents the redistribution from peripheral compartments [4].

$$u(t) = \delta(t) \cdot LD + \left(k_{10} + k_{12} \cdot e^{-k_{21} \cdot t} + k_{13} \cdot e^{-k_{31} \cdot t}\right) \cdot LD - \left(k_{21} \cdot x_2(0) \cdot e^{-k_{21t}} + k_{31} \cdot x_3(0) \cdot e^{-k_{31t}}\right) \quad (8)$$

The equation (8) was considered impractical [17] because, a virtually-time-free loading bolus was required and the solution of the differential equations may incur in precision discrepancies. The author suggests equations (6) and (7) [13], would be robust and accurate for IC.

The purpose of the current study is to implement these two different equations, (7) and (8) combined with Jacobs plasma concentration controller for the maintenance phase of anesthesia, and to compare them.

IV. MATERIAL AND METHODS

The present work aims at improving a previous version of ASYS [5], by implementing two TCI versions with different algorithms for the maintenance phase. An Asena GH MKIII pump from Alaris®Medical System was assessed and remotely controlled by our software [5]. The language used to develop the communication protocol for the monitor was LabVIEW 8.2 by National Instruments. The pharmacokinetic model used was Marsh [7] for the anesthetic drug propofol.

The versions of ASYS will be identifying as:

- Algorithm 1: ASYS with Alvis [13] equations (6,7) for continuous infusion integrated with Jacobs [15] concept to predicted and control Cpt.
- Algorithm 2: ASYS with Ting [17] equation (8) integrated with Jacobs [15] concept to predicted and control Cpt.

Both version were simulated and tested to evaluate their performance.

V. MAINTENANCE ALGORITHM

A. First Version - Maintenance Algorithm

This version was implemented with Algorithm 1 where the two equations combined represent the initial drug dose, equation (6), to reach the target concentration set, and the maintenance equation (7), to keep the target. To this algorithm was add a similar plasma controller of Jacobs [15]. Every 10s the rotine compared the real infused volume from the syringe pump and Cpt estimated from the model. The next plasma concentration and infusion rate will be calculated based in this feedback.

B. Second Version - Maintenance Algorithm

This version was implemented with Algorithm 2 with the equation (8) [17]. Considering the equation (8) at $time = 0$, the first term (LD) gives the initial bolus to fill the central compartment to reach the Cpt fast, followed for a constant infusion when $time \neq 0$ to keep the set target. To this algorithm a similar plasma controller of Jacobs [15] was added following what was described in the First Version.

A $70kg$ male patient was considered in both versions of ASYS for simulation. The profile 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.

VI. RESULTS

The Algorithms 1 and 2 were tested in simulation mode and compared. The version with Algorithm 1 started with a bolus infusion that was lower (relative error $-15,11\%$) than the bolus infusion administered by the version with Algorithm 2. Figure 2 shows that Algorithm 1 was slower (relative error 40%) than Algorithm 2 to reach $Cpt = 3$.

For the maintenance phase, where a Cpt of 5 had to be achieved, the version with Algorithm 1 also showed a delay in reaching the target, when compared to the version with Algorithm 2. When Cpt was setted at $5ug/ml$ Algorithm

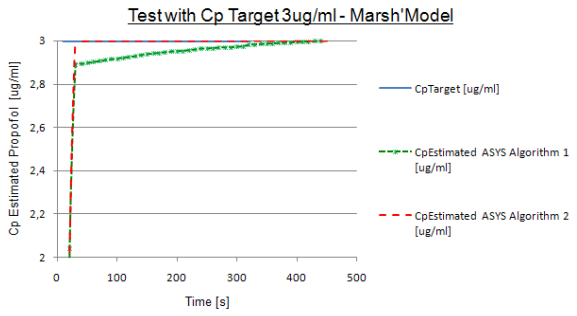

Fig. 2. Results from Algorithm 1 and 2 with Cpt=3g/ml.

1 presents a delay in maintenance phase, Fig 3, similar the delay presents with $Cpt = 3$. These results show that Algorithm 2 was more efficient than Algorithm 1 in both tests, allowing the target to be reached sooner in both situations

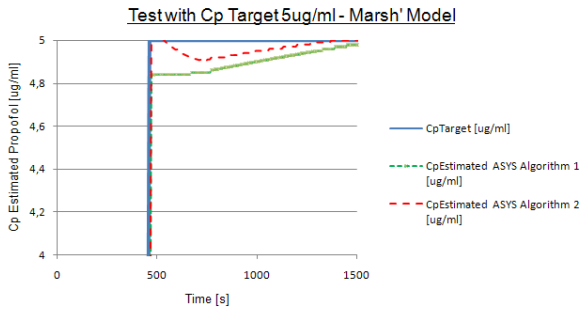

Fig. 3. Results from Algorithms 1 and 2 with Cpt=5g/ml.

VII. CONCLUSIONS AND FUTURE WORK

The differente system behavior presented by these two algorithms could be justify because of the initial drug dose given by equation (7) and (8). The Algorithm 2 was adopted as the more eficient IC for maintenance. Bressan [19] also presented results with ASYS and Algorithm 2 comparing it with the commercial system Orchestra Workstation and the Rugloop©software (Demed).These results [19] show a similar performance of ASYS similar and the commercial devices verifying the finding in the present work. This is an indicative to optimize the TCI controller developed and enhanced a new maintenance equation.

The future work will include the knowledge obtained with this two versions and [5], [18] to implement the algorithm to control effect-site concentration following the algorithm by Shafer [20]. The effect-site concentration control is more intensive computationally [6] but represents an efficient control of anesthesia for physicians and even because the plasma is rarely the site of drug effect[20].

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