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Investigating Applying Digital Deadbeat Controller to Automated Anesthesia Injection System

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Abstract: Anesthesia is not only important for surgery but also for intensive care. The anesthetic agent, e.g., a barbiturate is administered intravenous anesthesia to effect. Intravenous anesthesia provides rapid onset, stable maintenance and rapid recovery compared with inhaled anesthetics. The aim of this research was to investigate a reliable and safe controller for delivering automatic intravenous anesthesia system using simulated closed-loop control technology. Drug effect is measured during drug infusion in Closed Loop Anesthesia (CLAN). This may provide superior safety, better patient care and better quality of anesthesia whilst relieving the clinician of the need to make recurrent and minor alterations to drug administration. A new and generic mathematical model (Pharmaco Kinetic/Pharmaco Dynamics PK/PD) of the drug behavior inside the body was used in simulation of closed-loop control drug pumping. Deadbeat controller is used to control the drug pumping using the PK/PD patient's drug effect model and different parameters were investigated to determine their effects on the final response of the patient to the anesthesia. The investigated parameters are different levels limiter to limit the control signal (drug infusion) and the number of the digital bits used in the digital controller that affect the performance of the anesthesia system. These investigating lead to the best values which give best results. The CLAN system was tested using published data of virtual patients modeled. MATLAB\R2015 is used to simulate the proposed controller trying to reduce the dependency on external sensors as a feedback to the control system. The results were very optimistic which lead us to continue the work in the future using different controllers at a certain sequence to enhance the overall intravenous anesthesia performance.

Key words: Digital controller, Anesthesia feedback control system, patient's model anesthesia control system, external sensors, CLAN system, digital

INTRODUCTION

The major difficulty in the design of closed-loop control during anesthesia is the inherent patient variability due to differences in demographic and drug tolerance. These discrepancies are translated in to the Pharmaco Kinetics (PK) and Pharmaco Dynamics (PD). These uncertainties may affect the stability of the closed loop control system. This study aims at developing predictive controllers using deadbeat controller. This study develops patient dose-response models and to provide an adequate drug administration regimen for the anesthesia to avoid under or over dosing of the patients.

Modeling the patient response to anesthesia: Target Controlled Infusion (TLC) systems were introduced as a step toward automated anesthesia (Absalom, 2007). The TCI system depends on a patient model to compute an adequate infusion profile which is subsequently delivered to the patient intravenously by means of computer controlled infusion pump. A TCI system is an open-loop feed-forward controller. The anesthesiologist sets a target drug concentration in state of an infusion rate. This is either a blood plasma or effect site (brain) drug concentration, depending upon the TCI system (Al-Noor *et al*., 2016; Melani *et al*., 2016; Van-Poucke *et al*., 2004). It is clear that TCI systems are sensitive to model error and lack a mechanism to counteract disturbances. There are many TCI systems available on several markets where the dosing regimen has not yet obtained the FDA (the United States Food and Drug Administration) approval. Diprifusor is the oldest commercial TCI system that provides TCI propofol (Glen, 1998).

The closed-loop control drug dosing regimen is based on feedback from a measure of clinical effect

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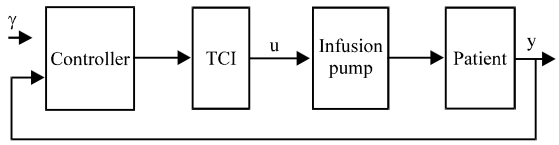

Fig. 1: Cassaded control of a TCL system

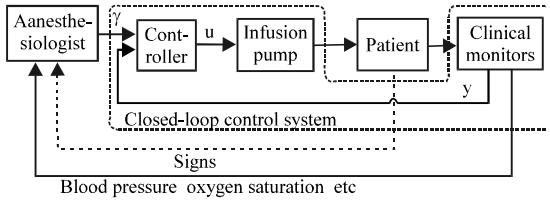

Fig. 2: Closed-loop control

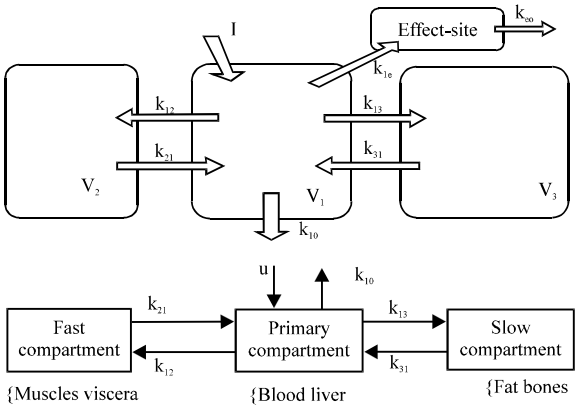

Fig. 3: Pharmacokinetic Model V_1: Volume 1, V_2: Volume 2, V_3: Volume 3, k_{ij}: constant rates

(Absalom *et al*., 2011; Bibian *et al*., 2005; Suksathan *et al*., 2016). In the literature there are two types of controllers reported; one in which the controller directly sets the infusion rate of a computer controlled infusion pump and the other one where the controller sets the target of a TCI system around which it is cascaded as showed in Fig. 1. The anesthesiologist still plays an important role when a closed-loop controlled drug dosing strategy is used. As showed in Fig. 2 the controlling role of the anesthesiologist, frequently adjusting the infusion profile or target concentration is handled by the feedback controller. However, the expertise of the anesthesiologist is still needed, e.g., to predict and counteract disturbances. Robust closed-loop controller can handle all these issues to some extent but there will always be outlier cases, requiring manual attention. There is also the possibility that manual attention is needed to resolve complications originating either from the surgery or the anesthesia itself or from equipment failure.

A lot of research related with automatic control of anesthesia has been made in the last decade where most of them use the intravenous drug propofol as the hypnotic agent. There are two trends of researches either signal-based control as PID (Liu *et al*., 2006; Dumont *et al*., 2009) and fuzzy controllers (Gil, 2004; Savkovic *et al*., 2017) or a model-based control, depending on the controller structure (Ionescu *et al*., 2008; Nino *et al*., 2009) the controlled variable (Struys *et al*., 2001; Furutani *et al*., 2005) and the prediction model used (Sreenivas *et al*., 2008; Syafiie *et al*., 2009; Sawaguchi *et al*., 2003). A comparative study between predictive control and PID techniques applied to the control anesthetic is done by Sreenivas *et al*. (2008).

It is clear from above that the TCI and closed-loop controlled drug dosing regimens rely on patient model; TCI relies directly on the model while the closed-loop approach relies on model indirectly to tune the controller. The most common model structure used to describe the redistribution, elimination and effect of anesthetic drugs can be decomposed into a series connection of a Pharmaco Kinetic (PK) Model relating drug infusion, distribution and elimination and a Pharmaco Dynamics (PD) Model, relating effect site concentration to clinical effect. This combined model is referred to as a PKPD model (Derendorf and Meibohm, 1999). Now a days, the PK/PD scheme has three compartments and the biophase (Hull, 1979) as shown in Fig. 3 where the volume V_1 is considered the blood compartment or central compartment; Volume 2 or 2nd compartment V_2, the fast or vessel-rich compartment and the Volume 3 or 3rd compartment V_3, the slow or vessel-poor compartment. The concentration in the central compartment is defined as the plasma Concentration (C_p).

The PK/PD Model simulates the drug behavior inside the body. 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. 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, so called central compartment from where it is distributed, metabolized and excreted. Pharmacokinetics describe what the body does to the drug (Johansen and Sebel, 2000):

$$PK \equiv G2a(s) = \frac{1\,(s+k_{21})\,(s+k_{31})}{V_1\,(s+p^1)\,\left(s+p^2\right)(s+p^3)}$$

PD phase: Part of the drug administered reaches the effect organ that is the organ where the drug will produce the desired clinical effect:

$$PD \equiv G2b(s) = keo/s+keo$$

Where:

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

$p_2 = k_{31}\times k_{21}+k_{13}\times(k_{12}+k_{21})+k_{10}\times(k_{21}+k_{31})$

$p_3 = k_{21}\times k_{31}\times k_{10}$

The plasma concentration (Gp (t)) is obtained by:

$$Gp(t) = \frac{M_1(t)}{V_1(t)}$$

where, $V_1 = V_c$, patient weight; V_c is a parameter from the PK Model. If I(t) = 0 t>0 the plasma concentration; (G_p (t)) is defined in time by:

$$Gp(t) = A\times e^{-\alpha\times t}+B\times e^{-\beta\times t}+G\times e^{-\gamma\times t}$$

Where:

A, B, C, a, β, γ = Thepharmacokinetics parameters

t = 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 (Chao, 2003) as follows:

$$Ce(t) = C_p(t)\left(1-e^{-keo\times t}\right)$$

$$C_e(s) = \frac{keo}{s+keo}C_p(s)$$

Deadbeat controller: A deadbeat controller is a digital controller that places all the closed loop poles in the origin (From the analog point of view, it is placing closed loop poles at s = -inf, since $z = e^{Ts}$, i.e., system reaches set point very fast). For n-zero poles, it guarantees that the system reaches the set point in n steps. The cost is that overshoot is usually very high and the control signal required may be expensive to generate. As such, it is only used in extreme situations such as weapons systems (Warwick, 1986). The deadbeat response has the following characteristics:

- Zero steady-state error
- Minimum rise time
- Minimum settling time
- <2% overshoot/undershoot
- Very high control signal output

MATERIALS AND METHODS

Proposed method: Based on the depth of anesthesia model (Soltesz, 2013) shown in Fig. 4, the proposed

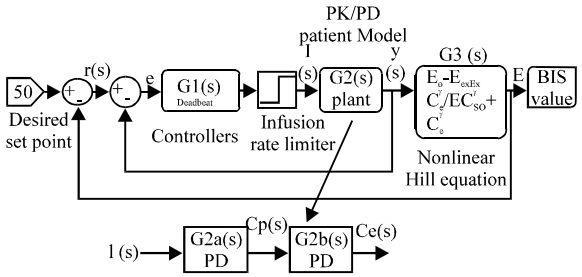

Fig. 4: Structure of DOA controller model

method of controlling the drug dosing is to apply the deadbeat controller in the internal path of the DOA system. Thus, the deadbeat controller is designed to eliminate the effects of the poles of the patients model PKPD (3 poles of PK Model and 1 pole of PD Model) to transform the transfer function of the controller from s-domain to z-domain. Tustin approximation (s = 2Tz-1/z+1) is used to transform the transfer function of the controller from s-z domain where T is the sampling period. The resultant transfer function in the z-domain is:

$$G_{c\ deadbeat}(s) = (s+p_1)\times(s+p_2)\times(s+p_3)\times(s+k_{e0})$$

$$G_{c\ deadbeat}(z) = \frac{\sum_{i=0}^{4} b_i z^{-i}}{\sum_{i=0}^{4} a_i z^{-i}}$$

Since, there are four poles to be deleted by the proposed controller and due to using the Tustin approximation then the order of the deadbeat controller is also four ($G_{c\ deadbeat}$ (z) illustrated above), so that the response of inner loop system must reach the input signal within four samples.

RESULTS AND DISCUSSION

The data is entered manually on the MATLAB spreadsheet. These data are collected and analyzed to establish the relative importance of each independent variable in the prediction. The data analysis results are integrated for model development. The models are developed and designed based on these data analysis and initial results presented. The performance of the proposed deadbeat controller is tested by using a step input as r(s). Nominal patient's data for DOA parameters of the PK/PD Model, showed in Table 1 were used to drive all the transfer functions of the inner loop of the DOA Model showed in Fig. 4 above where these functions were transferred from the s-z domain using Tustin approximation, so the resultant difference equations of each block of the inner loop using sampling step of 0.01 sec were computed by the simulation program written in MATLAB package.

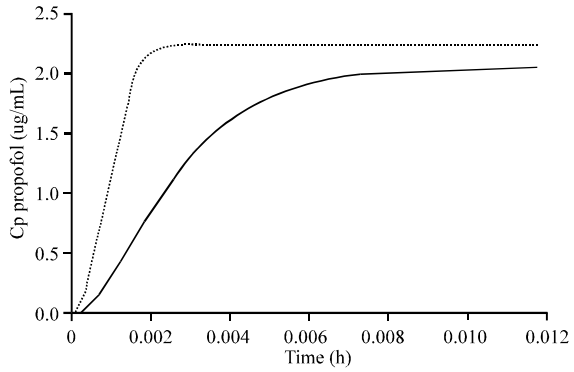

Fig. 5: Response V_1 values (15.9)

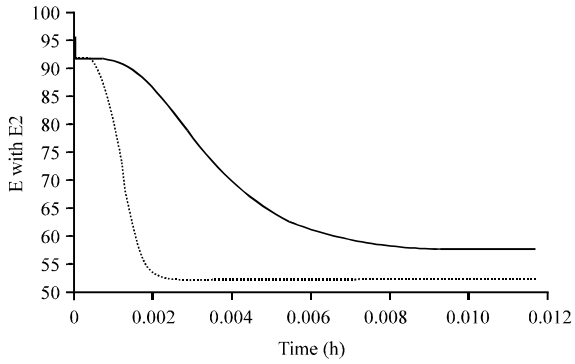

Fig. 6: Response the error with deadbeat controller

Table 1: Nominal patient's data for DOA parameters

Variables	Default values	Units
V_c	15.9000	L/kg
k_1	0.1190	m^{-1}
k_1	0.1120	m^{-1}
k_2	0.0550	m^{-}
k_1	0.0420	m^{-1}
k_3	0.0033	m^{-1}
k_e	0.2600	m^{-1}
E_5	2.5600	Ig/mL
γ	2.6510	None
$E_á$	92.0000	None
E_m	97.0000	None

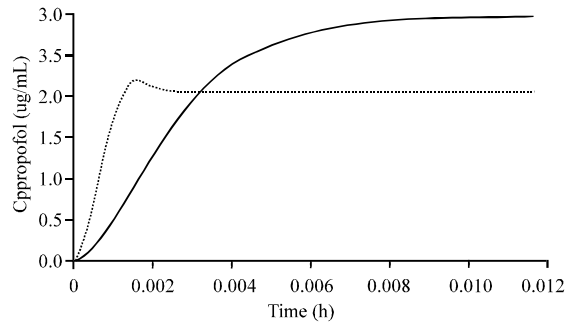

Fig. 7: Response V_1 values (10.9)

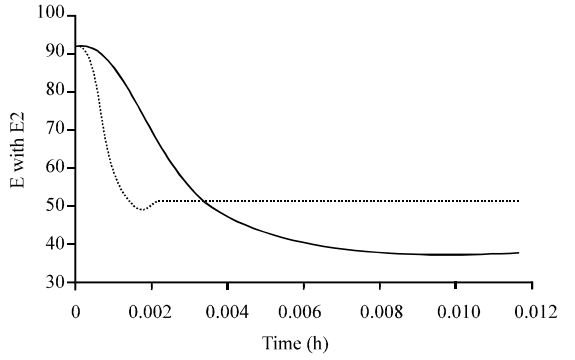

Fig. 8: Response the error with deadbeat controller

Since, the output of the deadbeat controller needs to be in the negative which cannot be applicable then a limiter is used to let the minimum control signal be equal to zero. Moreover, the maximum control signal may exceed the safe dose, so an upper limiter is also used where different values were tested to get the most proper one giving better response. The value of V_1 in G2a (s) above, affects the gain of the system then also different values were tested to get the most preferable value according to the response of the system for the used sampling frequency. According to these limitations, the output response of the inner loop system did not reach the input step input within 4 samples and there was an overshoot.

Moreover, the effects of using an ADC of specified number of bits (8-12) were studied using Root Mean Square (RMS) error technique. Figure 5 shows the response of the inner loop system for different V_1 values like (15.9) and (Fig. 6) the different response between the original error system and the error with deadbeat controller in same V_1. The response will be with (Fig. 7) illustrates the response of the inner loop system for different V_1 values like (10.9) and (Fig. 8) the different response between the original error system and the system error with deadbeat controller with the same V_1 where for each value of V_1 different upper limitation values were used. It is quite clear that the response of V_1 = (15.9) and for limitation of (2.651) is the best response and the Hill effective.

Moreover, the effect of using specified number of bits, 8 bit ADC, 10 bit ADC and 12 bit ADC were studied using Root Mean Square (RMS) error technique. Figure 9 shows the response of the system for the previous values of V_1 and upper limitation, found above with 8 bit ADC response when different length ADC. Figure 10 shows the response of the system for the

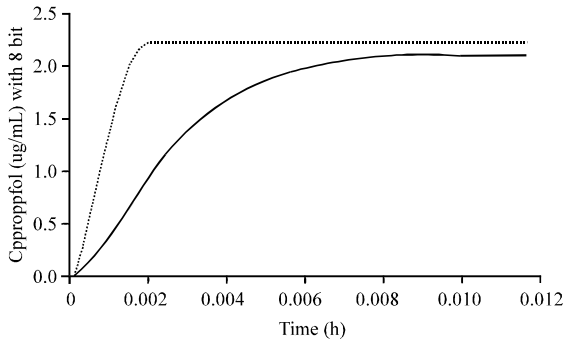

Fig. 9: The system with 8 bit ADC

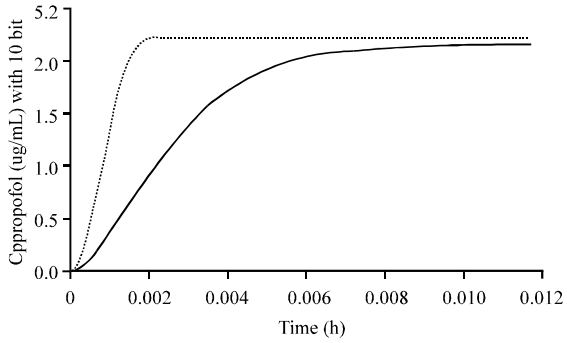

Fig. 10: The system with 10 bit ADC

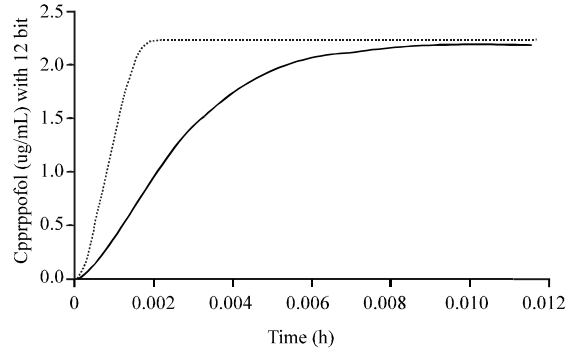

Fig. 11: The system with 12 bit ADC

previous values of V_1 and upper limitation, found above with10 bit ADC response. Figure 11 shows the response of the system for the previous values of V_1 and upper limitation, found above with 12 bit ADC response when different length ADC were used. It is obvious that the ADC of 12 bits is of less difference with respect to the response without ADC.

CONCLUSION

The results of applying deadbeat controller in the DOA Model system are optimistic and the value of V_1 found above is within the limits given in the literatures. To enhance the performance of the simulation one can use Rang-Kutta method to simulate the differential equations representing the PK/PD Model. In a future research, we proposed different controllers applied in a certain sequence to enhance the response.

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