Controlling the Depth of Anesthesia by Using Extended DMC

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Abstract- Monitoring and controlling the depth of anesthesia is really important, since over dosing and under dosing can be dangerous for the patients. Pharmacokinetic-Pharmacodynamic models vastly used for describing the relationship between input anesthetic agents and output patient endpoint variables. As there is a large variety between the patients so for controlling the depth of anesthesia we need a controller which should be robust enough and also because the anesthesia process is nonlinear and contains time delay, among them all the proposed methods for controlling the depth of anesthesia, model predictive controllers (MPCs) are good choices. Extended dynamic matrix control (EDMC) can be applied to nonlinear process control. In this method, control inputs are determined based on a linear model that approximates the process and is updated during each sampling interval. Science nonlinear relation still exists between the prediction error and the control input, numerical methods are used to solve the optimization problem defined in the method. The results showed that the performance of EDMC with or without presence of the noise and disturbance is better than GPC and also it is more robust.

Keywords - Anesthesia, Bispectral Index (BIS), EDMC, Pharmacokinetic-Pharmacodynamic model, Propofol

I. INTRODUCTION

Anesthesia can be defined as the lack of response and recall to noxious stimuli [1]. Anesthetists use a variety of observations, such as blood pressure, heart rate, lacrimation, movement, sweating, and pupil response, to make a judgment on DOA levels. The measure of anesthetic depth during surgical anesthesia has always represented a tough challenge and the experience of the anesthetists is required to control the patient’s anesthetic state [2]. Anesthesiologists act through the administration of a combination of anesthetics, opioid, and eventually, neuromuscular blocking agents. Propofol is an intravenous anesthetic agent which has gained considerable popularity over other agents because of its good solubility, short onset time, and quick recovery. It is also suitable for both induction and maintenance of anesthesia. Propofol is principally a hypnotic drug with no analgesic properties [3]. Here in this paper we consider propofol, thus our aim is to model and eventually control the hypnotic effect of this drug.

The effects of anesthetic drugs on the electroencephalogram (EEG) have been known since the early 40s. There are a number of signal processing tools and techniques available to quantify the EEG in order to derive a surrogate measurement of hypnosis [4]. Bispectral index (BIS) is the most notable one which appears to be closely related to the level of consciousness [5]. BIS is scaled between 0 and 100. A value of 100 represents the awake state. By increasing concentration of anesthetics, the index decreases. General anesthesia is obtained for an index between 60 to 40. Lower values represent deep hypnotic states [5]. The ease of Bispectral Index (BIS) monitoring and its ready availability in the operating room, opens the possibility of closed-loop control of anesthetic drug administration, using BIS as the performance and measurement variable [6].

Closed-loop control in medicine emerged as a serious contender for many forms of control in the late 1970s. It was pioneered by Sheppard et al. and Asbury et al., who demonstrated through clinical experiments that this form of control is safe, effective and in many cases better than manual control [7]. Up to now several methods has been introduced for controlling the depth of anesthesia [4]. Fixed gain controllers such as P, PI, PID strategies can perform well when used in clinical therapy and under certain conditions [8],[9], but on the other hand can lead to poor performances because of the large variability between subjects and the delay which exists in the model of the patient. Adaptive strategies cleverly overcome the problem of inter-intra patient's variability [10], [11]. In [5] a nonlinear adaptive controller has been used for controlling the BIS level. But they used some simplifications in their model. Lookuptables and fuzzy controllers have also been used for controlling depth of anesthesia [7], [12], [13]. In [13] they used some physiological signs such as SAP, HR, SW, LA and MO to evaluate the DOA level, but it seems these signs can't represent the DOA properly. Predictive control is a concept which enjoyed great popularity in the late 70's. In [2], they used Generalized Predictive Control (GPC) for controlling the DOA. They used physiological model and also MAP as a Sign of DOA. But it seems using other types of signals such as BIS or AEP are more valid for showing DOA level [7]. In [9] they used GPC for controlling paralysis and unconsciousness, the model they used wasn't complete.

Here in this research we use Extended DMC [14] for controlling the DOA level and it is explained in details in section II part B. DOA level is evaluated by BIS. The model we used is more complete comparing to the previous researches because of considering some individual parameters and it is introduced in section II part A. The result of the simulations is proposed in section III and in section IV the conclusions are reported.

II. CLOSED LOOP CONTROL OF ANESTHESIA

Automating the delivery of anesthetic drugs during surgery and controlling the drug effect improve the quality of control for acceptable level of Anesthesia, so it is clinically important. In order to design and implement closed loop control schemes, mathematical models of the patient and drug delivery system are required. In the following, the mathematical model used in this research and also the controller which has been used for controlling the DOA level, is explained.
A. Pharmacokinetic-Pharmacodynamic model

Drug dosing can be made more precise by using pharmacokinetic and pharmacodynamic (PK-PD) modelling. By relating dose to resultant drug concentration (pharmacokinetics) and concentration to the effect (pharmacodynamics), a model for drug dosing can be generated [4]. The standard modelling that has been commonly used to describe the relationship between anesthetic inputs and patient output indicators is that of compartment models [8]. Compartmental models, are dynamical models, typically assume that the body is comprised of more than one compartment. Within each compartment, the drug concentration is assumed to be uniform due to perfect, instantaneous mixing. Transport to other compartments and elimination from the body occurs through metabolic processes. Although the assumption of instantaneous mixing is an idealization, it has little effect on the accuracy of the model as long as we do not try to predict drug concentrations immediately after the initial drug dose [5]. A pharmacokinetic model of a drug is a mathematical expression relating the drug blood plasma concentration $C_p(t)$ to the administered dose $I(t)$. Here we consider a linear three-compartment model for intravenous anesthetic agent, propofol (Fig. 1). The mathematical expressions governing this model can be obtained by writing the mass balance equations:

\[
\dot{C}_1(t) = \frac{1}{V_1} I(t) + k_{12} C_2(t) + k_{13} C_3(t) - k_{10} C_1(t) - k_{12} C_1(t) - k_{13} C_1(t)
\]

\[
\dot{C}_2(t) = k_{12} C_1(t) - k_{21} C_2(t)
\]

\[
\dot{C}_3(t) = k_{13} C_1(t) - k_{31} C_3(t)
\]

\[
C_p(t) = C_1(t)
\]

Where $C_i$ is the drug concentration in compartment $i$, $k_{ij}$ is the rate constant governing the drug transfer from compartment $i$ to compartment $j$, $k_{10}$ is the rate of elimination, and $V_i$ is the volume of the central compartment [15].

In terms of propofol, the age, weight and Lean Body Mass (LBM) of the patients, the sampling site (venous or arterial) and the method of administration (bolus or infusion) were found to alter the PK parameters [6]. Understanding and quantifying these covariates reduce the model uncertainty. For considering these covariates in a model, Shuttler et al. in [16] propose a method for calculating PK parameters based on each individual. They used compartmental parameter set expressed as volumes and clearance ($V_{f1}, V_{f2}, V_{k1}, Cl_{f1}, Cl_{f2}, Cl_{k1}, Cl_{k2}, Cl_{k3}$). These sets are equivalent as they define the same PK relationship [6]. So according to [16], for calculating the PK parameters for each individual the age, weight, the sampling site and the method of administration should be asked and then the compartmental parameters based on volumes and clearances will be calculated.

\[
\frac{V_{f1}}{V_i} = \frac{k_{12}}{k_{21}} , \quad \frac{V_{f2}}{V_i} = \frac{k_{13}}{k_{31}} , \quad Cl_{f1} = Cl_{f2} = Cl_{f3} , \quad Cl_{k1} = Cl_{k2} = Cl_{k3}
\]

(2)

where $Cl_{ij}$ is the intercompartmental clearance and is defined by:

\[
Cl_{ij} = V_{ij} k_{ij}
\]

By using (2) and (3) the standard parameter set will be obtained.

An effect compartment is attached to the central compartment of the PK model to capture the complete response of the drug on specific endpoints (Fig. 1) [5], [6]. It was first introduced by Sheiner et al. in 1979; it is assumed that effect compartment receives a small mass of drug at a rate ($k_{e0}$) directly proportional to the central compartment drug concentration, which does not affect other time constant of the model. The drug exits this effect compartment in accordance with another rate constant $k_e$ [6]. In steady-state the concentration of this part can be related to the plasma concentration by the equation below:

\[
\frac{dC_e(t)}{dt} = k_{e0} (C_f(t) - C_e(t))
\]

where $C_f$ and $C_e$ are the plasma concentration and the concentration in the effect compartment, respectively [8]. According to what has been explained by Genty et al. in [15], a time delay in the form of $e^{-\gamma t}$ should be added to (4).

Pharmacodynamics models the relationship between drug concentration and effect. A sigmoidal $E_{max}$ function is used here to model the pharmacodynamic of the drug. The general form of this function is:

\[
E = E_{max} \cdot \frac{C_p(t)^{\gamma}}{E_{C50}^\gamma + C_p(t)^\gamma}
\]

where $E$ is the measured effect (e.g., BIS, HR, or MAP), $E_{C50}$ is the concentration of the drug at which half of the maximum achievable effect is observed in the patient, and the exponent $\gamma$ determines the degree of nonlinearity [17]. As mentioned earlier, BIS is one of the best indexes for evaluating the DOA level. In this research we use it as an observed effect of the patient. To model the BIS response to the propofol anesthetic, the specific $E_{max}$ function used is:

\[
BIS = \frac{BIS_0}{1 - \frac{C_p(t)^\gamma}{E_{C50}^\gamma + C_p(t)^\gamma}}
\]

where $BIS_0$ denotes the awake state, which is typically assigned a value of 100 [11].

According to [16], the PK model is obtained by knowing the age, weight of the patient and also the sampling site and the type of administration. For PD parameters we use the data gathered in [6] for 44 patients with different age.

B. Extended Dynamic Matrix Control (EDMC)

MPC families are vastly used in recent years because of their performance and simplicity [18]. To predict the process output and solve the optimization problem in a nonlinear MPC, high computational capability is required. This makes the approach impractical in some applications [14]. In the case of nonlinear problems, the exact solution of the optimization problem at every sampling instant is a difficult task. One of the efficient formulations tries to avoid the problems associated to non-convex optimization is Extended DMC, which is one of the simplest ways of dealing with...
process nonlinearities. The idea is to add a new term to the output prediction that tries to take nonlinearities into account [18]. In comparison with an ordinary DMC, this approach requires additional computations.

In EDMC, at each sampling interval, step responses of the nonlinear model of the process are determined. This is done by integrating equations of the nonlinear model twice. First by assuming zero future moves (which yields $Y_{\text{past}}$) and then by applying a step input with specified magnitude (which yields $Y_{\text{per}}$). Therefore,

$$g_i = \frac{Y_{\text{per}}(t+i) - Y_{\text{past}}(t+i)}{\delta}$$

where $\delta$ is the step magnitude and $g_i$ is the ith element of the step responses. Applying DMC formulation, when there is no constraints, the future control moves are calculated using the following equation:

$$\Delta U(t) = (G^T G + \lambda I)^{-1} G^T E(t+1)$$

(8)

where $G$ is a Toeplitz matrix constructed from step response samples ($g_i$) of the process.

$$G = \begin{bmatrix} g_0 & 0 & \cdots & 0 \\ g_1 & g_0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ g_{p-1} & g_{p-2} & \cdots & g_{p-m} \end{bmatrix}$$

$p$ and $m$ are control parameters and represent prediction and control horizons, respectively. $\lambda$ is the control move suppression coefficient. Vector $E$ consists of the output prediction errors, which is determined by the following equation:

$$E(t+1) = Y_d(t+1) - Y_{\text{per}}(t+1) - D(t+1) - D_{\text{nl}}(t+1)$$

(9)

$Y_d$ represents the desired output trajectory and is determined by passing the set point, $r$, through the following first-order filter.

$$y_d(t) = y(t)$$

$$y_i(t) = a y_i(t-i+1) + (1-a) r(t) \quad i = 1, \ldots, p$$

(10)

$$Y_i^r(t+1) = \left[ y_i(t+1), y_i(t+2), \ldots, y_i(t+p) \right]$$

$Y_{\text{past}}$ is free response of the model and is obtained by setting future moves equal to zero.

$$y_{\text{per}}(t+i) = \begin{cases} y_n(t+i) & \text{for } i < 0 \\ y_n(t+i)|_{\text{last}(\alpha)} & \text{for } i \geq 0 \end{cases}$$

(11)

$$Y_{\text{per}}^r(t+1) = \left[ y_{\text{per}}(t+1), y_{\text{per}}(t+2), \ldots, y_{\text{per}}(t+p) \right]$$

$D$ represents the future output differences of the process and its model,

$$d(t+i) = y(t+i) - ym(t+i), \quad i = 1, \ldots, p$$

$$D_i^r(t+1) = \left[ d(t+1), d(t+2), \ldots, d(t+p) \right]$$

(12)

Since process future outputs, $y(t+i)$, are not known in sampling time $t$, components of $D$ are assumed constant and set to the present error.

$$d(t+i) = d(t) = y(t) - y_n(t)$$

(13)

$D_{\text{nl}}$ stands for differences between the nonlinear and linear model outputs. Since both models are known in this case, $D_{\text{nl}}$ is known as well [17]. Comparing with DMC algorithm, this part is added to the error function. Equation (8) is solved in each sampling interval.

Here in this research we have some constraints in the form of (14), which caused us to obtain the control law by minimizing a cost function similar to the one in DMC.

$$-0.2 \leq U(t+j-1) \leq 0.2$$

$$0 \leq U(t+j-1) \leq 300 \frac{\text{mg}}{\text{min} \cdot \text{kg}}$$

(14)

Considering these constraints in control process is necessary because first of all the drug input can't be negative on the other hand the maximum effect of the drugs is defined so administration of a drug more than a special amount is useless. We used quadratic programming for calculating the control moves in each interval.

III. RESULTS

In simulation studies, we used the PK-PD model, which consider the covariates of the patients. Here the results just for a patient -34 year old and 58 kg woman- are shown. In the following simulation involving the infusion of the anesthetic drug propofol, we set $V_{\text{p}1}=7.7499 \text{l}$, $k_{10}=0.0027 \text{ s}^{-1}$, $k_{12}=0.0043 \text{ s}^{-1}$, $k_{21}=8.4682e-4 \text{ s}^{-1}$, $k_{21}=0.0018 \text{ s}^{-1}$, $k_{12}=5.198e-5 \text{ s}^{-1}$, $EC_{50}=3.6 \frac{\text{mg}}{\text{ml}^*}$, $\gamma = 2$, $T_d=4 \text{ s}$, and $BIS_0=100$. Consider that the desired target BIS is set at 50. The prediction horizon is 30 and control horizon is 5.

In Fig. 2., the response of EDMC and GPC can be compared, as it is shown that EDMC response is faster with lower settling time, and also the amount of drug for EDMC is less than GPC. In Fig. 3. a disturbance has been applied from $t=50$ to 150 sec., as it is clear EDMC response is smoother than GPC response in presence of disturbance, and also the total amount of drug in EDMC is less than GPC.

In Fig. 4 the performance of the controllers in presence of the noise with 0.1% magnitude is considered. Both of the controllers are robust, EDMC successfully works in presence of noise, although GPC performance is not that much bad. Additionally the effect of colored noise (not shown) is studied. The results showed that there isn't great difference between both controllers. Overlay, MPC methods are really effective for controlling the depth of anesthesia but considering the fact that in EDMC we need less drug for having same DOA comparing to GPC, it is much better to use EDMC instead of GPC.
IV. CONCLUSION

Using predictive controllers instead of manual control will optimize administration of the drugs. By using such controllers the anesthesiologist will be more confident about the level of DOA of the patients, so the safety will increase. Since, during surgery the presence of noise and disturbances are inevitable, using MPC for controlling the DOA which is a robust strategy, is a good choice. The simulations in previous section prove such a thing. Totally, by considering the nonlinearity of the process in designing EDMC, as we expect we can see a better response, better tracking and also a faster response in comparing with GPC and also in presence of noise and disturbance, EDMC performs better comparing the others such as GPC or PID.

REFERENCES


