Generalized Predictive Control of depth of anesthesia by using a pharmacokinetic-pharmacodynamic model of the patient

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Abstract—Monitoring and controlling the depth of anesthesia during a surgery is really important since over dosing and under dosing can be dangerous for the patients. The model which is used for describing the relationship between input anesthetic agents and output patient endpoint variables is pharmacokinetic-pharmacodynamic model which included the most significant covariates such as age and weight. Bispectral index (BIS) is one of the best criteria for evaluating the depth of Anesthesia. In this research we used BIS as a patient endpoint and Propofol as an anesthetic agent. As there is a large variety between the patients, we need a controller which should be robust against the disturbances and because the anesthesia process is nonlinear and contains a time delay, model predictive controllers (MPCs) seems act very well for it. In this paper we tried to use a constrained generalized predictive control (GPC) method for controlling the depth of Anesthesia. For comparison a PID controller has been designed. The results showed that the performance of GPC with or without presence of the noise and disturbance was much better than PID controller and also it was more robust.

Keywords-Anesthesia, Bispectral index, Generalized predictive control, Pharmacokinetic-Pharmacodynamic model, Propofol.

I. INTRODUCTION

Anesthesia can be defined as the lack of response and recall to noxious stimuli. This complex branch of the medical area is divided into three components: muscle relaxation, analgesia and unconsciousness [1]. Depth of Anesthesia (DOA) is one of the components of Anesthesia. 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.

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 hypnic 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 cheerfully overcome the problem of inter-intra patient's variability [10],[11]. In [5] a nonlinear adaptive control has been used for controlling BIS level. But they used some simplifications in their model. Lookup tables and fuzzy controllers has also been used for controlling depth of anesthesia [7],[12],[13]. Self Organized Fuzzy Logic Controllers (SOFLC) was used for controlling DOA. In [13] they used some physiological signs such as SAP, HR, SW, LA and MO to evaluate DOA, 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 GPC for controlling the DOA which is evaluated by BIS. The model we used is more complete comparing to the previous researches because of considering some individual parameters and it will be introduced in section 2. Section 3 will review the control algorithm of GPC, the result of the simulations is proposed in section 4 and in section 5 the conclusions are reported.

II. 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. The distribution of drugs in the body depends on transport and metabolic processes, many of which are poorly understood [4]. Different models have been proposed for modelling the drug effect, such as empirical models, compartmental models and physiological models [2]. The standard modelling paradigm that has been commonly used to describe the relationships 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 occur 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 $C_i(t)$ to the administered dose $I(t)$ [5]. Here we consider a linear three-compartment model for intravenous anesthetic agent propofol. The central compartment contains the arterial blood and highly perfused tissues such as brain and liver. Second compartment contains muscles and viscera, and a third compartment consists mostly fat and bones (Fig. 1). The mathematical expressions governing this model can be obtained by writing the mass balance equations:

$$\frac{dC_i(t)}{dt} = \frac{I(t)}{V_i} + k_{i2}C_2(t) + k_{i3}C_3(t) - k_{i1}C_i(t) - k_{i0}C_i(t)$$

$$\frac{dC_2(t)}{dt} = k_{12}C_1(t) - k_{21}C_2(t)$$

$$\frac{dC_3(t)}{dt} = k_{13}C_1(t) - k_{31}C_3(t)$$

$$C_p(t) = C_3(t)$$

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 $j$, $k_{i0}$ is the rate of elimination, and $V_i$ is the volume of the central compartment [14].

![Figure 1. Pharmacokinetics-pharmacodynamic compartmental model with the effect site][1]

In terms of propofol, the age, weight and Lean Body Mass (LBM) of 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 [15] propose a method for calculating PK parameters based on each individual. They used compartmental parameter set expressed as volumes and clearance ($V_j, V_2, V_3, Cl_1, Cl_2, Cl_3$), instead of standard compartmental parameter set ($V_1, k_{10}, k_{12}, k_{13}, k_{21}, k_{31}$). These sets are equivalent as they define the same PK relationship [6].

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 ($k_{1e}$) 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 $k_{e0}$ [6]. In steady-state the concentration of this part can be related to the plasma concentration by the equation below:

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

Where $C_1$ 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 [14], a time delay in the form of $e^{-td}$ should be added to (2).

Pharmacodynamics models the relationship between drug concentration and effect. Commonly used PD models are fixed-effect models, linear models, log-linear models, $E_{max}$ models, and sigmoidal $E_{max}$ models. PD models are used to express the relationship between the drug effect and drug concentration. A sigmoidal $E_{max}$ function is used here to model the pharmacodynamic of the drug. The general form of this function is:

$$E(t) = E_{max} \frac{E_{max}}{1 + \frac{C(t)}{EC_{50}}}$$

[1]: https://example.com/image1.png
\[ E = E_{\text{max}} \cdot \frac{C_e(t)^\gamma}{EC_{50}^\gamma + C_e(t)^\gamma}, \] (3)

Where \( E \) is the measured effect (e.g., BIS, HR, or MAP), \( EC_{50} \) 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 [16]. 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 \( E_{\text{max}} \) function used is:

\[ BIS = \text{BIS}_0 \left( 1 - \frac{C_e(t)^\gamma}{EC_{50}^\gamma + C_e(t)^\gamma} \right), \] (4)

where \( \text{BIS}_0 \) denotes the awake state, which is typically assigned a value of 100 [11]. This PD model is nonlinear, and for using GPC algorithm which will describe in next section, a linear model is needed so we should linearize the model around its set point.

According to [15], the PK model is obtained by knowing the age, weight of the patient, the sampling site and also the type of administration. For PD parameters we use the data gathered in [6] for 44 patients with different age.

III. GENERALIZED PREDICTIVE CONTROL

Manual control by anesthesiologist can be tedious, imprecise, time consuming and sometimes of poor quality, depending on his skills and judgment. Underdosing in patient may causes pain and awareness during surgery, while overdosing may result in delayed recovery from anesthesia and also may result in respiratory and cardiovascular collapse. Closed-loop control may improve the quality of drug administration, lessening the dependence of patient outcome on the skills of the anesthesiologist [11]. As anesthesia contains delay and there are also some constraints which should be considered on the infusion and the rate of infusion drug so it seems the controllers belong to MPC family are good choices. Here we use generalized predictive control (GPC) for controlling DOA level. The predictive control developed in this research study is based on the GPC strategy introduced by Clark et al. in [17] and [18].

Most single-input and single-output plants, when considering operation around a particular set point and after linearization, can be described by:

\[ A(z^{-1})y(t) = z^{-d}B(z^{-1})u(t-\tau) + C(z^{-1})e(t) \] (6)

Where

\[ A(z^{-1}) = 1 + a_1z^{-1} + a_2z^{-2} + \cdots + a_nz^{-n}, \]
\[ B(z^{-1}) = b_0 + b_1z^{-1} + b_2z^{-2} + \cdots + b_nz^{-n}, \]

\[ C(z^{-1}) = c_0 + c_1z^{-1} + c_2z^{-2} + \cdots + c_nz^{-n}. \]

\( u(t) \) and \( y(t) \) are control input and output sequences of the plant and \( e(t) \) is a zero mean white noise. And \( d \) is the dead time of the system. The controller computes the vector of controls using optimization of a function of the form:

\[ J(N_1, N_2, N_u) = \sum_{j=0}^{N_u} \delta(j)[\hat{y}(t+j|t) - w(t+j)]^2 \]
\[ + \sum_{j=1}^{N_2} \lambda(j)[\Delta u(t+j-1)]^2, \] (7)

Where \( N_1 \) is the minimum costing horizon, \( N_2 \) is the maximum costing horizon, \( N_u \) is the control horizon, \( w \) is the future set-point, \( \delta(j) \) and \( \lambda(j) \) are the weighting sequences. The aim of predictive control is to keeps the output as near as \( w \), for this purpose (7) should be minimized by considering the constraints defined in (8) [3]. For solving (7) we used quadratic program in MATLAB.

\[ -0.2 \leq \Delta u(t+j-1) \leq 0.2 \]
\[ 0 \leq u(t+j-1) \leq 300 \frac{\mu g}{ml.min.kg} \] (8)

Considering these constraints in controlling the process is necessary because first of all, the drug input can't be negative and on the other hand the maximum effect of the drugs is defined so administration of a drug more than a special amount is useless.

IV. SIMULATION RESULTS

The simulation studies used the PK-PD model which considers the covariates of the patients. Here the results just for a patient who was a 34 year old and 58 kg woman are shown. In the following simulation involving the infusion of the anesthetic drug propofol, we set \( V_1=7.7499 \text{ s}^{-1} \), \( k_{12}=0.0043 \text{ s}^{-1} \), \( k_{21}=8.4682 \text{ kg/ml} \), \( k_{13}=0.0018 \text{ s}^{-1} \), \( k_{31}=5.198e-5 \text{ s}^{-1} \), \( EC_{50}=3.6 \text{ kg/ml} \), \( \gamma=2 \), \( T_0=4 \text{ s} \), and \( \text{BIS}_0=100 \). Consider that the desired target BIS is set at 50. The prediction horizon is 30 and control horizon is 5. Even though PID controller shows faster response in first few seconds but it is clear in Fig. 2 that the output of GPC reaches the set point faster than the output of PID controller and the amount of administered drug in GPC control is much more robust and it is shown in Fig. 4 a step disturbance added to the output at \( t=100 \text{ s} \) while there is a mismatching in \( V_1 \).

V. CONCLUSIONS

By the use of predictive control instead of manual control, drug administration will be optimized. By using such controllers the anesthesiologist will be more confident of the level of DOA of the patients so the safety will increase. Since, during surgery the presence of noise and disturbances are inevitable, using GPC for controlling the DOA which is a robust strategy, is a good choice. The simulations in previous
section prove such a thing. Totally, GPC in comparing PID performs better in encountering the delay. Although PID showed a good tracking of the set point but the amount of drug calculated by this controller is much more than the drug needed for GPC controller.

REFERENCES


Figure 2. BIS of the patient when using PID controller & GPC controller.

Figure 3. Administered drug when using PID controller & GPC controller.

Figure 4. BIS of the patient when using PID & GPC controller and a step disturbance added to the output at t=100 s while there is a mismatching in V1.