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Model Predictive Control for Intravenous Anaesthesia

Nisha Sugathan[1], Sreekala Devi .K[2]

PG Student, Department of EEE, Lourdes Matha College of Science and Technology, Kuttichal, Kerala, India[1]

Associate Professor, Department of EEE, Lourdes Matha College of Science and Technology, Kuttichal, Kerala, India[2]

Abstract: Anaesthesia plays a very important role in surgery and in the intensive care unit. It is defined as a reversible pharmacological state of patient where hypnosis, analgesia, and muscle relaxation are guaranteed. Automatic control of anaesthesia is incorporated in order to minimize the effort of doctors. To estimate the drug effect in the patient's body and calculate the corresponding drug infusion rates patient models are used. Due to the inherent complexity and variability of the patient dynamics difficulty in obtaining a good model is high. A detailed compartment mathematical model featuring pharmacokinetic model and Pharma co dynamics model is used to represent the distribution of drugs in the body. The pharmacokinetic model represents the relation between the drug administration and drug concentration in the body whereas the Pharma co dynamics model represents the relation between the concentration of the drug in the central compartment and the effect observed on the patient.

Keywords: Aaesthesia, mp-MPC, BIS

I. INTRODUCTION

Anaesthesia plays a important role in surgery and in the intensive care unit (ICU). It is defined as a reversible pharmacological state of the patient where hypnosis, analgesia, and muscle relaxation are guaranteed [1]. Analgesics block the sensation of pain; hypnotics produce unconsciousness, while muscle relaxants prevent unwanted movement of muscle tone. The role of the anaesthetist has become more complex and indispensable to maintain the patients' vital functions before, during, and after surgery. To estimate the drug effect in the patient's body and calculate the corresponding drug infusion rates, average population models are used. These strategies may not always be safe for the patient since they do not take into accountancy measured variable in a feedback control scheme and even if they reach the desired level of sedation fast, it can result in unsafe minimal values [1]. In stress situations, the anaesthetist has to deal with routine assessments and simultaneously solve complex problems quickly. The automation of some routine actions of the anaesthetist reduces the workload and consequently increase the safety of the patient.

MPC is a model-based control technique that calculates the optimal control action considering constraints on the input, output, and state variables by solving an optimization problem. The downside of this control technique is that the optimization problem has to be solved online. One way to avoid this is to use explicit/multi parametric MPC, which solves offline the optimization problem using multi parametric programming and derives the control inputs as a set of explicit functions of the system states. An important advantage of the multi parametric model predictive control (mp-MPC) is that the previously offline computed control laws can be easily implemented on embedded controllers. These types of devices use programming languages that cannot support powerful mathematical computations.

II. PATIENT MODEL

A compartmental model is used to describe the PK–PD blocks representing the distribution of drugs in the body, i.e., mass balance. The PK model represents the relation between the drug administration and drug concentration in the body, whereas the PD model represents the relation between the concentration of the drug in the central compartment and the effect observed on the patient. In each compartment, the drug concentration is assumed tobe uniform, as perfect and instantaneous mixing is assumed. The structure of the compartmental model is depicted in Fig. 1.

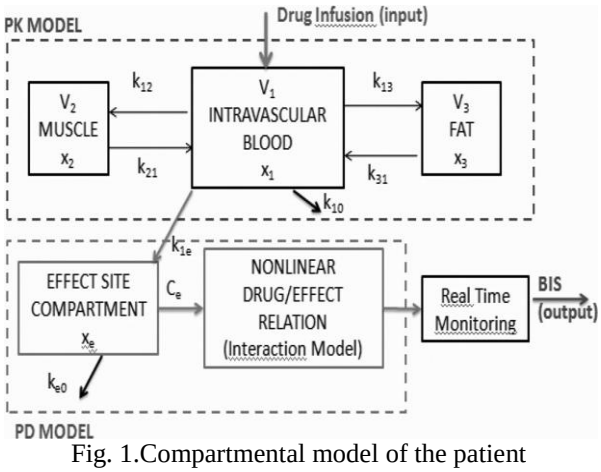

Fig. 1.Compartmental model of the patient

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Pharmacokinetic compartmental 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. For simplicity, the transport rate is often assumed to be proportional to drug concentration. 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. In a simple one-compartment model, the body is assumed to consist of a single compartment in which instantaneous mixing occurs, followed by elimination. It is usually assumed that elimination is linear, with the rate of elimination directly proportional to the drug concentration in the compartment. This model is characterized by two parameters: the compartmental volume and the elimination rate constant . In contrast to pharmacokinetic modeling, Pharma co dynamic modeling is less readily related to molecular processes.

The molecular mechanism of action of many drugs is well understood; most drugs act by binding to a receptor on or within target cells. There is a well-developed theory of multiple equilibrium binding of ligands, such as drug molecules, to receptors on larger macromolecules, such as proteins. In theory, Pharma co dynamics, which models the relationship between drug concentration and effect, should follow from models of molecular binding. However, the physiological effect is an interplay of numerous factors, and it is generally not possible to analytically relate the drug effect at the level of the intact organism to the number of receptors bound by the drug at the molecular level. Empirical models are thus needed. It might be assumed that drug effect is proportional to the drug concentration at the effect site, but this simple linear model is unrealistic since it admits the possibility of limitless drug effect as drug concentration increases while ignoring saturation effects. The PK–PD models most commonly used for Propenol are the fourth-order compartmental model anaesthesia. PK describes the distribution of the drug in the human body.

$$\dot{x}_1(t) = -\frac{[k_{10} + k_{12} + k_{13}]x_1(t) + k_{21}x_2(t) + k_{31}x_3(t) + u(t)}{V_1}$$

$$\dot{x}_2(t) = k_{12}x_1(t) - k_{21}x_2(t)$$

$$\dot{x}_3(t) = k_{13}x_1(t) - k_{31}x_3(t)$$

$$\dot{x}_e(t) = -k_{e0}x_e(t) + k_{1e}x_1(t) \quad (1)$$

where x_1 represents the drug concentration in the central compartment [mg/L]. The peripheral compartments 2 (muscle) and 3 (fat) model the drug exchange of the blood with well and poorly diffused body tissues. The concentrations of drug in the fast and slow equilibrating peripheral compartments are denoted by x_2 and x_3, respectively. The parameters k_{ij} for ij, denote the drug transfer frequency from the ith to the jth compartment, and u(t) [mg/min] is the infusion rate of the anaesthetic or analgesic drug into the central compartment. The parameters of the PK models depend on age, weight, height, and gender and can be calculated for Propofol.

$$V_1 = 4.27\ (l)$$

$$V_2 = 18.9 - 0.391\ (age - 53)(l)$$

$$V_3 = 2.38\ (l)$$

$$C_{l1} = 1.89 + 0.456\ (weight - 77) - 0.0681\ (lbm - 59) + 0.264\ (height - 177)(l/\min)$$

$$C_{l2} = 1.29 - 0.024\ (age - 53)(l/\min)$$

$$C_{l3} = 0.836\ (l/\min)$$

$$k_{10} = \frac{C_{l1}}{V_1}^{-1} (\min)$$

$$k_{12} = \frac{C_{l2}}{V_1}^{-1} (\min)$$

$$k_{13} = \frac{C_{l3}}{V_1}^{-1} (\min) \quad (2)$$

$$k_{21} = \frac{C_{l2}}{V_2}^{-1} (\min)$$

$$k_{31} = \frac{C_{l3}}{V_3}^{-1} (\min)$$

$$k_{e0} = 0.456^{-1} (\min)$$

where C_{l1} is the rate at which the drug is cleared from the body, and C_{l2} and C_{l3} are the rates at which the drug is removed from the central compartment to the other two compartments by distribution. The lean body mass (lbm) for men (M) and women (F) are calculated by:

$$lbm\_M = 1.1 * weight - 128 \frac{weight^2}{height^2}$$

$$lbm\_F = 1.07 * weight - 148 \frac{weight^2}{height^2} \quad (3)$$

The drug concentration in this compartment is represented by x_e , called the effect-site compartment concentration. The effect compartment receives drug from the central

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compartment by a first-order process and it is considered as a virtual additional compartment. Therefore, the drug transfer frequency for Propenol from the central compartment to the effect site compartment is considered in clinical practice to be equal to the frequency of drug removal from the effect-site compartment $k_{e0} = k_{1e} = 0.456\ [\min^{-1}]$. When considering the drug effect observed on the patient, the bispectral index(BIS) variable can be related to the drug effect concentration Cabby the empirical static nonlinear relationship called also the Hill curve.

$$BIS(t) = E_0 - E_{\max}\frac{C_e(t)^{\gamma}}{C_e(t)^{\gamma} + EC_{50}^{\gamma}} \quad (4)$$

The inverse of the Hill curve can be defined by:

$$C_e(t) = EC_{50}\left(\frac{E_0 - BIS(t)}{E_{\max} - E_0 + BIS(t)}\right)^{\frac{1}{\gamma}} \quad (5)$$

Here $C_e = x_e . E_0$ denotes the baseline value (awake state—without drug), which by convention is typically assigned a value of 100, $E_{\max}$ denotes the maximum effect achieved by the drug infusion, EC_{50} is the drug concentration at 50% of the maximal effect and represents the patient sensitivity to the drug, and γ determines the steepness of the curve.

III. CONTROL SCHEME

MPC is a control methodology based on two main principles: explicit online use of a process model to predict the process output at future time instants, and the computation of an optimal control action by minimizing one or more cost functions, including constraints on the process variables. The main differences between the different types of MPC algorithms are: the type of model used to represent the process and its disturbances and the cost functions to be minimized, with or without constraints.

Multi parametric programming is a technique to solve an optimization problem, where the objective is to minimize or maximize a performance criterion subject to a given set of constraints where some of the parameters vary between specified lower and upper bounds. The main characteristic of the mp-MPC is its ability to obtain: 1) the objective and optimization variable as a function of the varying parameters, and 2) the regions in the space of the parameters where these functions are valid [critical regions (CR)] .This reduces the online implementation of the MPC to simple function evaluation, facilitating real-time applications. For the mp-MPC, the generic optimization problem solved is:

$$\begin{aligned}\min_{x,y,z}\ J &= x_N' P x_N + \sum_{k=1}^{N-1} x_k Q_k x_k \\ &+ \sum_{k=1}^{N-1} (y_k - y_k^R)' QR_k (y_k - y_k^R) \\ &+ \sum_{k=0}^{N_u-1} (u_k - u^R)' R_k (u_k - u^R) \\ &+ \sum_{k=0}^{N_u-1} \Delta u_k R1_k \Delta u_k \end{aligned} \quad (6)$$

$$\begin{aligned} x_{t+1} &= Ax_t + Bu_t \\ y_t &= Cx_t \\ BIS_{\min} &\le y \le BIS_{\max} \\ \Delta u_{\min} &\le \Delta u \le \Delta u_{\max} \\ x_t &\in x \subseteq R^P, u_t \in u \subseteq R^S \end{aligned} \quad (7)$$

where x are states, y are outputs, and u are controls, all (discrete) time-dependent vectors. The subsets of output variables that get tracked have time-dependent set points y^R. Finally, Δu are changes in control variables, $\Delta u(k) = u(k) - u(k-1)$. The prediction horizon is denoted by N and control horizon by N_u. X and U are the sets of the state and input constraints that contain the origin in their interior. Both Q > 0, the objective coefficient for the states and P > 0, the terminal weight matrix for the states, are symmetric semi positive definite matrices. The quadratic matrix for manipulated variables R > 0 is a symmetric positive matrix, QR is the quadratic matrix for tracked outputs, and R1 is a weight matrix for the control action changes (Δu). The control problem is posed as a quadratic convex optimization problem for which an explicit solution can be obtained as follows:

$$u = f(x) = \begin{Bmatrix} K_1 x + c_1, x \in CR^1 \\ K_s x + c_s, x \in CR^s \end{Bmatrix} \quad (8)$$

where s is the number of CR.

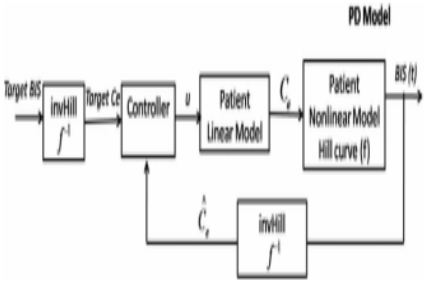

Fig. 2 MPC control scheme.

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The presence of the Hill nonlinearity complicates the use of linear controller synthesis. Two methods to overcome this problem have been proposed: Exact and local linearization. Exact linearization is based on the compensation of the nonlinearity introduced by the Hill curve, in the PD model. Since the Hill nonlinearity is a monotonic function (f) of the normalized effect site concentration, it has an inverse. Using a parameter scheduling technique, the inverse Hill function (f^{-1}) could be implemented in the controller as illustrated by the block diagram in Fig. Here, f is using the nonlinearity parameter of the real patient (E_0 , E_{max} , EC_{50} , γ), while f^{-1} is using the parameter assumed by the controller (the nominal patient nonlinearity parameters a priori known (E_0 mean , E_{max} mean , EC_{50} mean , γ mean). The controller aims at controlling the estimated drug concentration $\hat{C}_e$, which is straight-forward, using a linear controller. An exact linearization occurs only in the case where the patient model is identical to the nominal model in which case it completely cancels the nonlinearity and $\hat{C}_e = C_e$. The local linearization is based on the linearized PK–PD model for a BIS value of 50. An important challenge of DOA control is the high inter and intra-patient variability. This results in different dynamics in PK model, and changes in the parameters of the Hill function for each patient model.

IV. SIMULATION RESULT

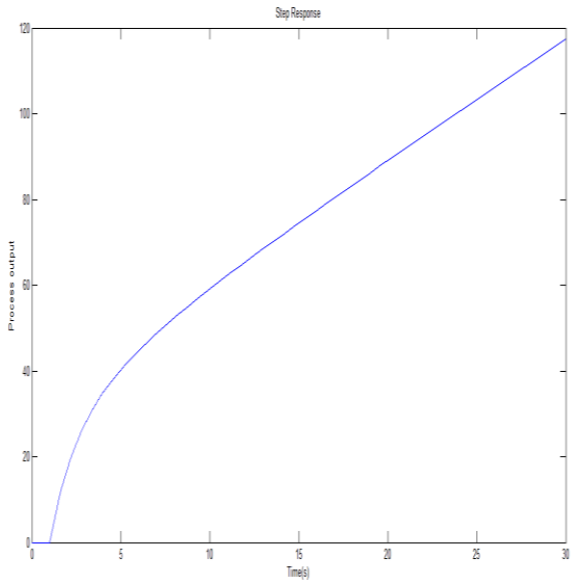

Fig .3 Response with an uncompensated system

The response of an uncompensated system is very poor. Whereas the response with multi parametric model predictive controller gives better response. The results show a high efficiency, optimal dosage, and robustness of the MPC algorithm to induce and maintain the desired BIS reference while rejecting typical disturbances from surgery. The mp-MPC approach, which is an offline optimisation method, has similar performances with the online method and promising results.

V. CONCLUSION

Multi parametric model predictive controller shows better performance. The main advantage of multi parametric model predictive controller is its ability to solve offline as well as online problems.mp-MPC shows better response. In biomedical field efficiency is the most important factor. mp-MPC is a better solution for such problems.

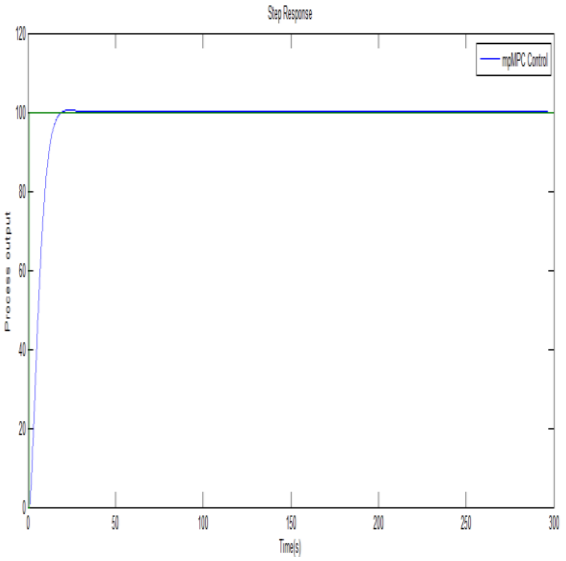

Fig .4 Responses with mp-MPC

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