Hypnosis regulation in presence of saturation, surgical stimulation and additional bolus infusion ⋆

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Abstract: The closed loop regulation of hypnosis implies the mixed effect of the actions dictated by a software based controller, and by the expert knowledge of the anesthesiologist. Other effects such as slew rate limitations due to resolution limits or saturation of the pump infusion system are also present in practice. Almost without exception, the actions of the anesthesiologist and other hardware limitations are not taken into account by the software based controller, hence they are regarded as disturbances. In this work, a PID controller is implemented to investigate the effects of such additional features in the closed loop dynamics. The results are discussed based on simulation study on a linear patient dynamic model.

Keywords: internal model control, PID control, hypnosis, anesthesia, biomedical engineering, robustness, saturation, rate limiter

1. INTRODUCTION

A manifold of regulatory loops have been proposed in the last decade for drug dosing problems, e.g. diabetes (Kovacs, 2017a,b; Kovacs et al., 2013), anaesthesia (Lemos et al., 2014; Merigo et al., 2017), etc. Drug intake, uptake and clearance have been characterized using either compartmental models, either input-output filters by means of linear transfer functions (Soltesz et al., 2013). In the framework of individualised treatment, irrespective of the medical application, it is important to deliver patient models which are sufficiently accurate yet simple in structure such that adaptation may be obtained (Nino et al., 2009). Optimal control response for hypnosis has shown that no unique controller can be used to ensure the desired performance over both induction and maintenance phases of general anesthesia (Padula et al., 2017).

The complete regulatory paradigm is however much more complex than anything literature addresses from control engineering point of view. The computer based drug dosing optimisation is always limited in the information it receives from the system (i.e. the amount of vital signals fed back from the patient into the control algorithm). Nevertheless, in general anaesthesia, the anesthesiologist provides a cocktail of optimal dosages of various drugs to induce and maintain this complex physiological state in the patient, while avoiding under- and over-dosing, and coping with great patient variability (Neckebroek et al., 2013).

Effects of rate limiters, saturation, or additional bolus infusion from the anesthesiologist which are *invisible* to the control algorithm can induce degradation in the closed loop performance (Ionescu et al., 2017). In this way, often conclusions that closed loop may be inadequate for hypnosis regulatory loop are based on poor settings of the context in which controllers may be tested and compared against manual practice or other controllers. Also, open loop target controlled infusion algorithms developed and tuned by non-control experts may result in unnecessarily high order complexity of nonlinear function adaptation, e.g. the adaptation of the Hill curve response to the actual patient response during the induction phase (De Smet et al., 2008).

Since any drug regulatory loop is seen as an operator guide and never let in full autonomous operation, the clinical expert will always have a supervisory role and intervene whenever necessary. From a control engineering viewpoint, the action of the anaesthesiologist is based on information which is not available to the controller. For instance, the controller sees only the hypnotic state of the patient, past values and past drug dosing samples, makes a prediction for optimizing the best suitable dosing scenario to reach/maintain the desired level of hypnosis. The anaesthesiologist, however, has a broader view of information, from the various sensing devices monitoring vital signs of the patient, e.g. heart rate, respiratory rate, distal oxygenation, and can anticipate effects in the hypnotic state from this information cocktail.

In this paper, we present a robust formulation of a model based control algorithm for hypnosis regulation to include and analyse the hardware limitation effects on the overall loop performance. Also, the rationale for introducing the

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anesthesiologist-in-the-loop dynamics is given and tested in simulation.

2. CASE STUDY: HYPNOSIS REGULATORY LOOP

As an important part of the anaesthesia paradigm, hypnosis is characterized by unconsciousness, i.e. inability of the patient to recall intra-operatory events. In order to control the depth of anesthesia by means of model-based control strategies, a suitably defined model which captures the dynamics of the relation between drug uptake, drug effect and the patient is required (Nascu et al., 2015; Ionescu et al., 2015).

The selection of the model input and output variables is crucial for achieving optimal control (Bibian et al., 2015; Ionescu et al., 2014). The pharmacokinetic/pharmacodynamics model most commonly used for propofol is the 4th order compartmental model described in (Bibian et al., 2015). This model is generically represented in figure 1, where the most important elements for control purposes and relevant actions for hypnosis level controls are presented. Usually, the three compartments are referred to as blood, muscle and fat, in the order of time constants. The usual differential equations balancing the drug diffusion and clearance rates among these compartments can be simplified to linear input-output relations, e.g. represented as tranfer functions whose dynamics are governed by zero-pole values (Soltesz et al., 2013). The dynamics of patient response up to the Hill curve is thus a simplified 4th order transfer function, whose parameters depend on the patient's biologic characteristics.

This 4th order patient model we will represent as $P(s) = \frac{B(s)}{A(s)}$, with s the Laplace operator, and B, A polynomials with coefficients relating the input $u(t)$ (Propofol, i.e. hypnotic drug, infusion rate) to output $C_e(t)$ (concentration in the 4th, intermediate compartment). The relation between the concentration in this 4th compartment and the measured effect signal, i.e. the Bispectral Index (BIS) is modelled as a nonlinear sigmoid Hill curve scaled between 0%-100%, with 100% denoting fully awake patient:

$$BIS(t) = E_0 - E_{max}\frac{C_e^{\gamma}(t)}{C_e^{\gamma}(t) + C_{50}^{\gamma}} \tag{1}$$

where E_0 is the BIS value when the patient is awake; E_{max} is the maximum effect that can be achieved by the infusion of Propofol; C_{50} is the Propofol concentration at half of the maximum effect and γ is a parameter which together with the C_{50} determines the patient sensitivity to the drug. E_0 and E_{max} are considered equal to the value of 100. The BIS signal has proved most suitable in clinical trials for regulatory closed loops in hypnosis (Absalom and Kenny, 2003), although it induces artificial time delays from the signal processing algorithm (Ionescu et al., 2011) and alternative, delay free signals have been proposed (Bibian et al., 2011). An important factor in the origin of great uncertainty in patient PD model is the great patient variability (Padula et al., 2016).

3. INTERNAL MODEL CONTROL BASED PID TYPE REGULATOR

The Internal Model Control (IMC) philosophy relies on the Internal Model Principle, which states that control can be achieved only if the control system encapsulates, either implicitly or explicitly, some representation of the process to be controlled and has the general structure depicted in Figure 2 (Bequette, 2002). In this figure, d is an unknown

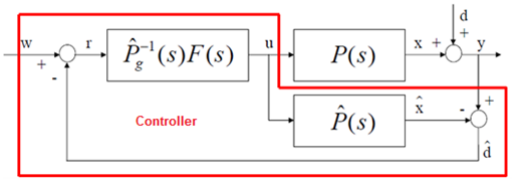

Fig. 2. Schematic representation of an IMC compensated closed loop

disturbance affecting the system. The manipulated input u is introduced to both the process and its model. The process output, y, is compared with the output of the model $\hat{x}$, resulting in a signal $\hat{d}$. If the process is well known then a perfect estimation of the disturbances will be reached.

An important step in IMC control design is to avoid unstable or noncausal compensator transfer function by adding a filter $F(s)$ to make the compensator proper (Bequette, 2002), and separate the model in "invertible" and "non invertible" transfer functions in order to design the controller.

A suitable choice for the filter $F(s)$ is:

$$F(s) = \frac{1}{(1+\lambda s)^n} \tag{2}$$

with n such that $C(s)$ is (semi-)proper and λ a tuning parameter (related to the closed-loop speed). This choice is suitable for a step setpoint and step disturbance at the output of the process.

IMC implies a more complicated structure of the closed loop, however for implementation it is possible to represent it, as a general transfer function. The transfer function of the controller in the general form is presented in (3) and the closed loop is presented in (4).

$$R(s) = \frac{\hat{P}_g^{-1}(s)F(s)}{1 - \hat{P}_g^{-1}(s)F(s)\hat{P}(s)} \tag{3}$$

$$Y(s) = \frac{\hat{P}_g^{-1}(s)F(s)P(s)}{1 + \hat{P}_g^{-1}(s)F(s)(P(s) - \hat{P}(s))}W(s) + \\ + \frac{1 - \hat{P}_g^{-1}(s)F(s)\hat{P}(s)}{1 + \hat{P}_g^{-1}(s)F(s)(P(s) - \hat{P}(s))} \tag{4}$$

with $\hat{P}_g(s)$ the invertible part of the process. This representation in closed loop of the IMC algorithm is given in figure 3.

Assuming that the process model can be approximated as a second order minimum-phase system without time delay Bequette (2002):

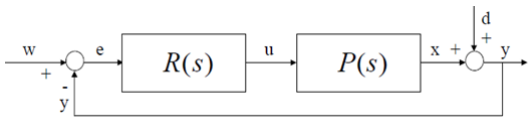

Fig. 3. Generic scheme of the IMC in closed loop form.

$$P(s) = \frac{K(\beta s + 1)}{(\tau_1 s + 1)(\tau_2 s + 1)} \tag{5}$$

the parameters for the equivalent PID controller with filter are obtained:

$$C(s) = K_p(1 + \frac{1}{Tds + 1} + T_i s)\frac{1}{\beta s + 1} \tag{6}$$

with

$$K_p = \frac{\tau_1 + \tau_2}{\lambda K}; T_i = \tau_1 + \tau_2; T_d = \frac{\tau_1 \tau_2}{\tau_1 + \tau_2} \tag{7}$$

Introduce the notation

$$Q(s) = \hat{P}_g^{-1}(s)F(s) \tag{8}$$

with $F(s)$ suitably chosen. The equivalent transfer function of the IMC controller as from figure 3, can be written as:

$$R(s) = \frac{Q(s)}{1 - Q(s)\hat{P}(s)} \tag{9}$$

with $R(s)$ replaced by the PID type controller structure.

4. ADDITIONAL ELEMENTS IN THE LOOP

It is useful to take into account a-priori hard nonlinear limitations, such as saturation and slew rate, when dealing with real-life processes. For instance, pump flow rate limiters, changing pump (zero saturation), or maximal flow rate of the pump (full saturation). Also, the fact that the pump can only inject drug and not taking it back (positive system) is an important challenge for control. In this case, only the infusion dynamics can be controlled, at various rate frequencies, whereas clearance is fixed, for each patient in particular, by his/her own biological characteristics.

In terms of process dynamics, these limitations are in fact part of the process. If they are not known to the operator, then the controller will not be aware of their existence in the process and error may accumulate, leading to the integrator wind-up effect. In the context of IMC, the controller design requires an invertible, stable part of the process. If this inversion of the process needs to be avoided, an equivalent feedback structure must be developed in order to allow inherent feedback inversion.

5. SIMULATION ANALYSIS RESULTS

As from (Soltesz et al., 2013), a generic formulation for the patient dynamic response model can be given as:

$$P(s) = K\frac{(s + z_1)(s + z_2)}{(s + p_1)(s + p_2)(s + p_3)(s + p_4)}e^{-}Ls \tag{10}$$

with the gain K, the delay L and zeros z_i and poles p_i related to the biological characteristics of the patient. For the purpose of our study, these precise values are not important, hence their derivation is left for the interested reader in (Soltesz et al., 2013). We have used the following values for representing the patient model: $z_1 = -10$, $z_2 = -15$, $p_1 = -1$, $p_2 = -0.8$, $p_3 = -0.02$, $p_4 = -0.5$, $K = -0.005$ and a sampling period of $T_s = 1$ second. From here a simplified approximation to the structure from (5) is extracted with the following parameters:$z_2 = -15$, $p_1 = -1$, $p_2 = -0.8$, and $K = 0.005$. Although the time delay has been neglected in this study, it has been shown to vary significantly in clinical settings and thus challenge the control performance (Ionescu et al., 2011).

Since the effects we are going to discuss are related to dynamic response in closed loop, the concentration-to-effect relation from (1) has been omitted from this study.

The comparison is done between an uncompensated way (i.e. the limitations are not taken into account) and in a compensated way (limitations are apriori taken into account and numerically implemented in controller output), in discretized form at sampling period of 1 second. In the PID controller parameters, the tuning parameter $\lambda = 15$ has been used.

5.1 Resolution and Saturation Effects

Here we compare the results obtained for limitations in the resolution of the pump infusion rates and limit saturations in the minimal and maximal delivered values.

The first case situation is for a resolution of 0.001/100 mg/ml/second and a saturation of 0-0.02 mg/ml/second. Figure 4-top depicts the input-output signals for the generic PID as $R(s)$ closed loop scheme and figure 4-bottom for the compensated anti-windup and resolution case. We can observe the undershoot present in the uncompensated scheme due to saturation effect. The effect of actuator resolution limitation (i.e. slew rate limitation) is seen at the output as an oscillation around the desired reference value.

Next, we re-do the same test for an improved actuator resolution, i.e. 0.0001/100 mg.ml.second. The corresponding results are given in figure 5.

5.2 Surgical Stimulation Effects

A realistically designed surgical stimulus disturbance profile has been developed based on clinical expertize as depicted in figure 6. The closed loop response is given in figure 7 for the resolution 0.0001/100 mg/ml/s and saturation 0-0.02 mg/ml/s.

5.3 Anesthesiologist-in-the-loop Effect

To mimic the effect of anesthesiologist-in-the-loop, the following rationale has been applied. In practice, the anesthesiologist *sees* other vital signs of the patient (i.e. blood pressure, heart rate, respiratory rate, etc) and based on this information he acts with additional bolus injection. Also, if he/she expects that specific intervention taking place in the next instants will likely arouse the patient from its hypnotic state, he anticipates its effect by additional bolus injection. In control engineering terms,

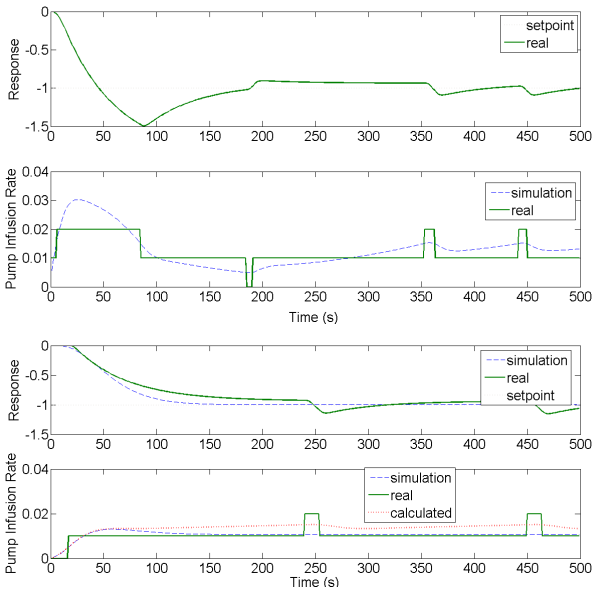

Fig. 4. Uncompensated (top) and compensated (bottom) IMC scheme - results for resolution 0.001/100 mg/ml/s and saturation 0-0.02 mg/ml/s.

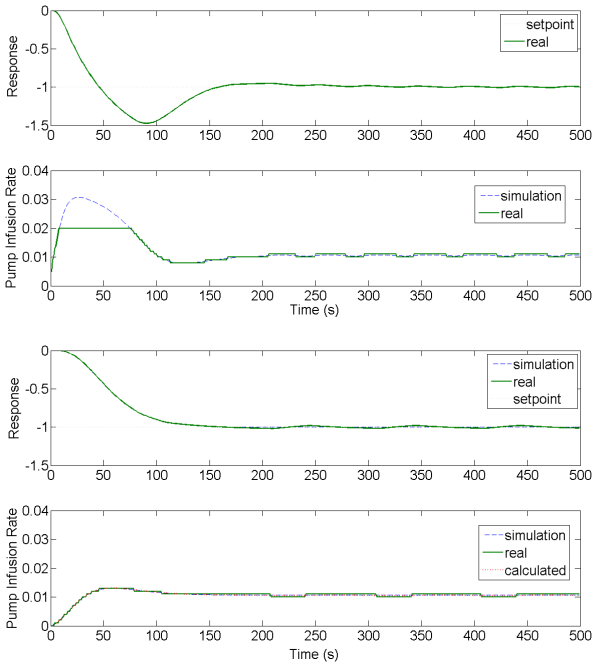

Fig. 5. Uncompensated (top) and compensated (bottom) IMC scheme - results for resolution 0.0001/100 mg/ml/s and saturation 0-0.02 mg/ml/s.

this bolus injection represents a feedforward action at the process input, aimed to compensate for a future disturbance present at the output of the process. The potential bolus infusion added by the anesthesiologist-in-the-loop is depicted along with the surgical stimulation profile in figure 8. The closed loop performance in this case is depicted in figure 9, for resolution 0.0001/100 mg/ml/s and saturation 0-0.02 mg/ml/s.

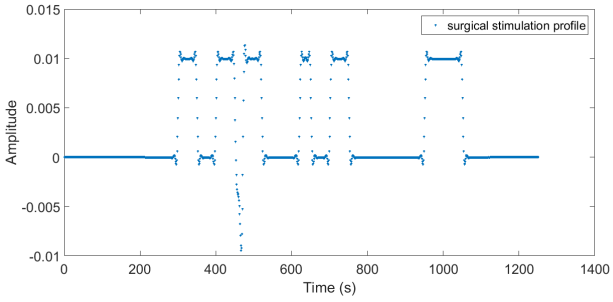

Fig. 6. Surgical stimulation profile as disturbance signal.

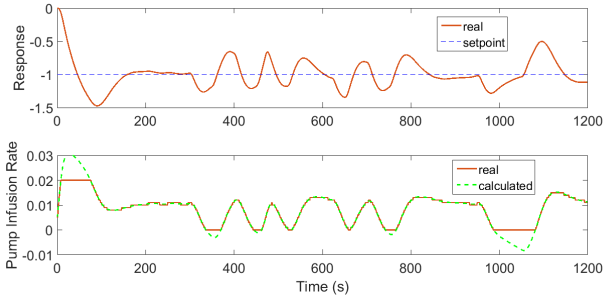

Fig. 7. Disturbance rejection in closed loop.

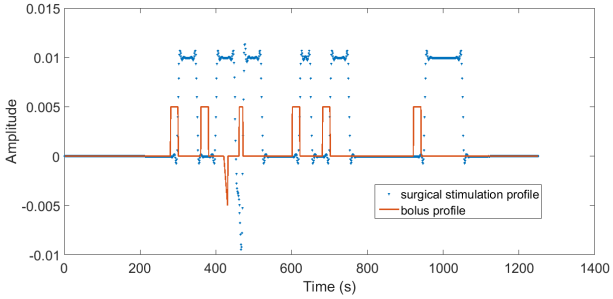

Fig. 8. Additional bolus infusion profile from the anesthesiologist-in-the-loop and the surgical stimulation profile as disturbance signals.

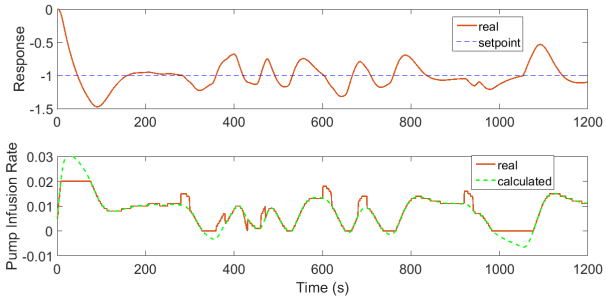

Fig. 9. Disturbance rejection in closed loop with additional bolus infusion from anesthesiologist-in-the-loop.

5.4 Discussion

From all comparison tests above, it can be concluded that a smoother convergence of the control effort (i.e. pump infusion rates) is achieved with the proposed compensated IMC scheme. This may be beneficial from the point of view of avoiding sudden bursts into the infusion rates values, leading to minimized over-dosing risk. Although not taken

into account explicitly by the proposed controller, the actions of the anesthesiologist, i.e. the additional bolus infusion, is robustly perceived by the control scheme such that performance in closed loop is improved.

The actions of the anesthesiologist-in-the-loop may be suitably translated in a meaningful disturbance filter information in a model predictive control strategy. Such a model based control algorithm (MPC), is a more natural choice than feedback based control since the anesthesiologist also reacts in an anticipatory context, as discussed in (Ionescu et al., 2017). A manifold of surgical procedures have well defined steps, which could be implemented in a control loop as part of process model (i.e. patient and surgeon). The combination between the two players is not addressed yet in control literature, but it is necessary in order to improve performance in presence of surgical stimuli.

6. CONCLUSION

This paper addressed the problem of resolution and saturation limits during hypnosis regulation. Additional effect of anesthesiologist-in-the-loop has been analysed. The simulation results indicate that the closed loop performance may benefit from more detailed mimicking of the true clinical practice, while overall clinical practice may benefit from the advantages of using closed loop control (e.g lower infusion rates, smoother rates, minimal risk for overdosing, etc).

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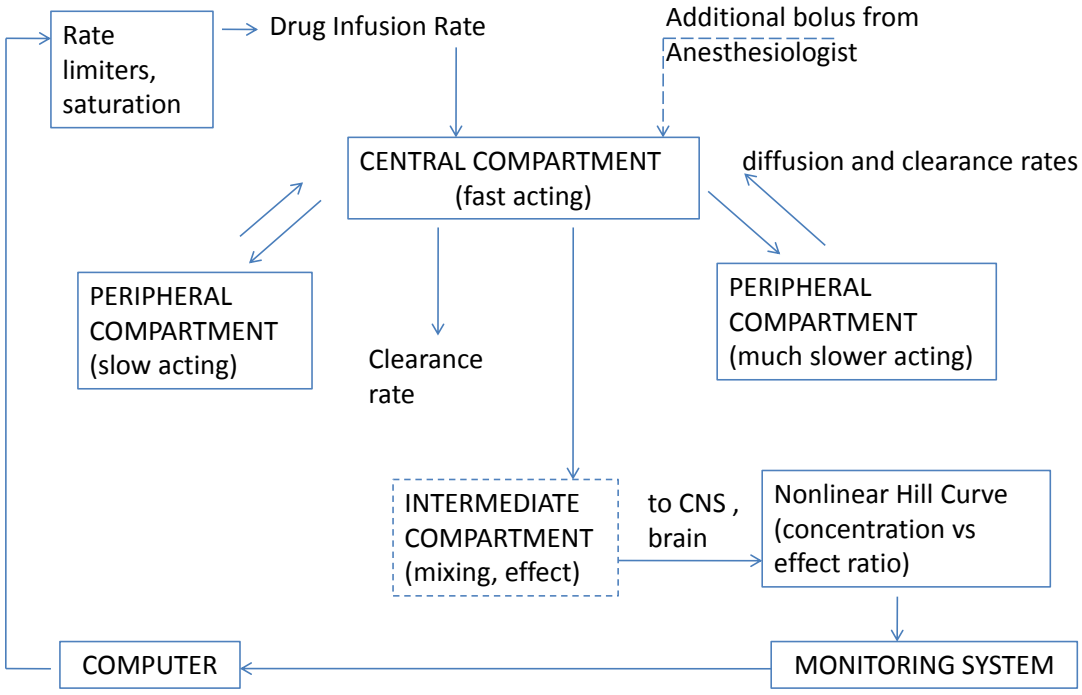

Fig. 1. A schematic representation of a closed loop infusion control with anesthesiologist-in-the-loop.