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Pharmacodynamic Modelling of Drug-Induced Ventilatory Depression and Automatic Drug Dosing in Conscious Sedation

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Abstract— **In conscious sedation (CS) procedures, the patient is sedated but retains the ability to breathe spontaneously. Drug-induced ventilatory depression represents a dangerous side effect of CS, possibly leading to hypoventilation and subsequent hypoxia. In this work, we propose a new pharmacodynamic model for drug-induced ventilatory depression. The model presents a parsimonious structure and shows good agreement with experimental data for different drugs. In addition, we explore the innovative idea of regulating drug infusion during CS by means of a feedback control system based on measurements of transcutaneous partial pressure of CO_2. In simulations, the controller proves able to maintain a predefined target of CO_2 despite pain, external disturbances and inter-patient variability in the sensibility to the drug. The implementation of the controller during CS procedures would improve clinical practice minimizing the occurrence of drug-induced ventilatory depression by tailoring drug infusion to patient's needs.**

Index Terms— **pharmacodynamic modelling, automatic drug dosing**

I. Introduction

Conscious sedation (CS) is defined as a "state of sedation that allows patients to tolerate unpleasant procedures while maintaining adequate cardiorespiratory functions and the ability to respond purposefully to verbal command" [1]. CS is employed in clinical practice to provide patient analgesia and anxiolysis for a wide range of medical treatments, e.g. endoscopy, lithotripsy, cystoscopy. However, although CS is a well-established clinical procedure, it is far from being unproblematic. Often, CS is performed with opioids, which are known to exert a dose-dependent depressant effect on ventilation. An excessive dose of opioid may result in respiratory arrest imposing risk of hypoxic brain damage, therefore representing a primary cause of morbidity [1]. Conversely, an inadequate amount of opioid may result in patient discomfort, injury because of lack of cooperation or adverse physiologic response to stress. In this context, the administration of the exact amount of opioid to achieve the desired therapeutic effect while preserving the spontaneous respiratory drive represents a critical issue. The problem is further complicated by a pronounced inter-individual variability in the sensibility to the drug, making experience-based dosing extremely ineffective.

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Titration of opioid infusion according to ventilation measurements, like respiratory rate and/or minute ventilation, is not feasible, as these measurements are usually noisy and extremely artifact prone. However, the partial pressures of respiratory gases might represent a surrogate measurement for ventilation. By depressing ventilation, opioids induce tissue hypoxia and hypercapnic acidosis. Innovative sensors have been recently introduced, which combine pulse oximetry with transcutaneous detection of CO_2 partial pressure, thus indirectly measuring the adequacy of ventilation [2]. The aim of this work is to explore the potentiality of introducing an automatic feedback controller to tailor opioid infusion during CS to individual needs based on these novel sensors. The goal of the controller is to administer analgesic doses of drug maintaining ventilation at an adequate level despite external painful stimulations and disturbances, extreme inter-individual variability and pharmacologic impairment.

For successful control design, acquaintance with the dose-to-effect relationship of pharmacologic ventilatory depression is required. Although drug-induced respiratory depression is a well-known dangerous side effect of opioids, only few attempts have been made at modelling its pharmacodynamics (PD) [3], [4], [5]. In 2004, Magosso and coworkers proposed a description of the human ventilatory system in the presence of the respiratory depressant fentanyl (*Magosso Model*) [5]. To date, the Magosso Model is the most comprehensive representation of the physiological mechanisms involved in ventilation control available. The accuracy of the physiological description implemented in the Magosso Model, however, comes at the cost of a rather complex formulation, with a large number of parameters of difficult identification. Therefore, the first challenge of this work is to derive a novel PD model of drug-induced ventilatory depression (*New Model*) that overcomes the limitations of the Magosso model, requiring the estimation of a fewer number parameters and allowing their direct estimation from experimental dose-effect data for different opioids.

II. Methods

A. Pharmacodynamic Modelling

Both the Magosso Model and the New Model are based on a model of the human ventilatory system proposed by Ursino and coworkers (*Ursino Model*) [6]. Therefore, let us first summarize the most relevant aspects of this model. The Ursino model comprises three interconnected subsystems: the *gas exchange system*, the *cardiovascular regulation* and the *ventilatory regulation*, as illustrated in Figure 1. For

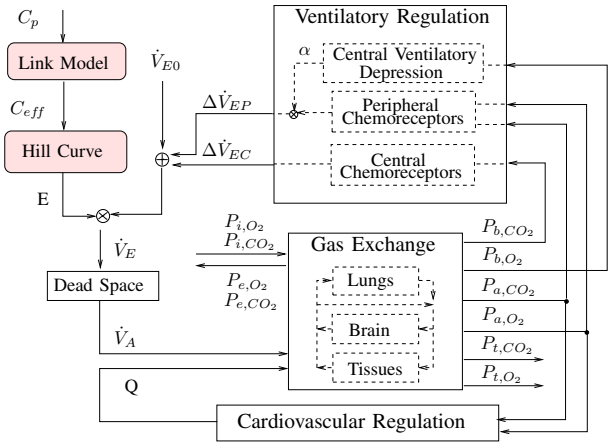

Fig. 1. Schematic representation of the Ursino Model [6] and its extension to include the effect of respiratory depressants in accordance with the New Model. Shaded blocks denote the effect of the drug according to Eq. (5) and (6). C_p and C_{eff} are the drug plasma and effect-site concentration, respectively. E is the drug effect on ventilation. P_{i,O_2}, P_{e,O_2}, P_{a,O_2}, P_{b,O_2}, P_{t,O_2} are the inspired, expired, arterial, brain and tissue partial pressures of oxygen, respectively. Analogous notation is used for CO_2. $\dot{V}_E$ is the minute ventilation, $\dot{V}_{E0}$ the basal value, $\dot{V}_A$ is the alveolar ventilation. $\Delta\dot{V}_{EP}$ and $\Delta\dot{V}_{EC}$ reflect the influence on ventilation of the peripheral and central chemoreceptors, respectively. The term α models the central hypoxic ventilatory depression. Q is the cardiac output.

the purposes of this work, let us focus on the ventilatory regulation, the subsystem that modulates ventilation as result of changes in O_2 and CO_2 partial pressures. In the Ursino Model, minute ventilation ($\dot{V}_E$) results from the superposition of three regulatory mechanisms: the peripheral chemoreceptors, the central chemoreceptors and the central hypoxic ventilatory depression, according to the following equation [6]:

$$\dot{V}_E = \max\ \left\{\dot{V}_{E0} + \alpha \cdot \Delta\dot{V}_{EP} + \Delta\dot{V}_{EC},\ 0\right\} \tag{1}$$

where $\dot{V}_{E0}$ is the basal value of minute ventilation, the multiplicative term α refers to the central ventilatory depression (equal to 1 in basal conditions). $\Delta\dot{V}_{EP}$ and $\Delta\dot{V}_{EC}$ are the changes in minute ventilation produced by the peripheral and central chemoreceptors, respectively.

In the Magosso Model, the Ursino Model is extended to comprise the depressant effect of fentanyl on ventilation. The pharmacologic effect is modelled as an attenuation factor on base-line ventilation and on the chemoreceptors, as described by the following equations [5]:

$$\dot{V}_E = \max\ \left\{\dot{V}_{E0} - K(C_f) + \alpha \cdot \Delta\dot{V}_{EP} + \Delta\dot{V}_{EC},\ 0\right\} \tag{2}$$

$$\frac{d\Delta\dot{V}_{EP}(t)}{dt} = \frac{1}{\tau_p}\left[-\Delta\dot{V}_{EP} + A(C_f)\cdot G_p\left[f_{pc}(t-D_p) - f_{pc0}\right]\right] \tag{3}$$

$$\frac{d\Delta\dot{V}_{EC}(t)}{dt} = \frac{1}{\tau_c}\Big[-\Delta\dot{V}_{EC} + A(C_f)\cdot G_c \cdot \left[P_{b,CO_2}(t-D_c) - P_{b,CO_20}\right]\Big] \tag{4}$$

where C_f stands for fentanyl plasma concentration, τ_p (τ_c), G_p (G_c) and D_p (D_c) are the time constant, the static gain and the time delay of the low-pass filter used to model the peripheral (central) receptors. f_{pc0} is the basal value of the activity in the peripheral chemoreceptive afferent fibres and P_{b,CO_20} stands for CO_2 partial pressure in the brain in basal conditions. $K(C_f)$ and $A(C_f)$ represent the attenuation factors on base-line ventilation and the receptors, respectively. In the absence of drug, the attenuation factors equal 1 and Eqs. (2)-(4) correspond to the Ursino Model. The attenuation factors depend on C_f via a static relationship and a first order low-pass dynamic. Overall, the Magosso Model requires the estimation of seven drug-dependent parameters. Moreover, discriminating between the pharmacologic effect on base-line ventilation and that on the receptors is unfeasible from experimental dose-effect data. Little evidence of the influence of respiratory depressants on the single ventilation control mechanisms control can be found in the literature. Therefore, in the New Model we suggest to represent the drug effect as a single global outcome term, as observed experimentally. In this way, model complexity and number of parameters are drastically reduced. Figure 1 illustrates the proposed model structure. Drug effect is modelled as an attenuation factor acting on ventilation as suggested by Bouillon and coworkers [4]. The global PD is modelled by means of a link model [7] and a Hill curve [7]:

$$\frac{dC_{eff}}{dt} = k_{e0}\cdot(C_p - C_{eff}) \tag{5}$$

$$E = \left(1 - E_{max}\cdot\frac{{C_{eff}}^{\gamma}}{{C_{eff}}^{\gamma} + {EC_{50}}^{\gamma}}\right) \tag{6}$$

where k_{e0} is the mass transfer constant between the plasma drug concentration (C_p) and the drug concentration at the effect-site (C_{eff}), characterizing the time delay between C_p and effect. E is drug effect, E_{max} the maximal effect achievable, EC_{50} the effect-site drug concentration producing 50% of E_{max}, and γ a parameter modulating the steepness of the resulting sigmoidal curve. By normalizing the maximal effect achievable (E_{max}=1), the New Model requires the determination of only three parameters that can be easily estimated from experimental data. To assess the reliability of the New Model in reproducing experimental results, we estimate the model parameters via a least-square procedure from clinical data for three different opioids commonly used in CS: fentanyl, alfentanil and remifentanil. Literature data are used for fentanyl [5] and remifentanil [4]. For alfentanil we use experimental data provided by the University Hospital in Bern relative to ten patients receiving a 1 mg bolus of drug.

B. Controller Design and Test

The global structure for controller design and testing is illustrated in Figure 2. The transcutaneous CO_2 measurement provided by the sensors has been found to deviate very little from arterial CO_2 partial pressure (P_{a,CO_2}) during transients and to present a negligible offset at steady-state [2]. Therefore, P_{a,CO_2} is used in the following as input to the controller instead of a transcutaneous CO_2 signal that is not explicitly modelled at this stage. Due to the fast on- and off-set of effect, remifentanil is the drug of choice for controller design. In accordance to clinical experience, a P_{a,CO_2} of 50 mmHg

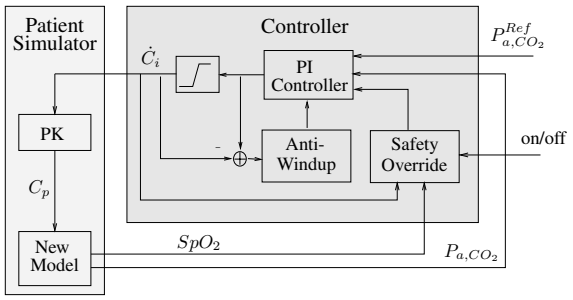

Fig. 2. Set-up for controller design and test. P^{Ref}_{a,CO_2} is the reference value of CO_2 arterial partial pressure, SpO_2 is the oxygen saturation, on/off represents the switch for starting/stopping automatic control, $\dot{C}_i$ is the drug infusion rate and C_p the corresponding drug plasma concentration.

corresponds to analgesic remifentanil concentrations [8]. Of course, depending on the clinical goal, different set-points can be selected. This value is therefore selected as reference for the controller (P^{Ref}_{a,CO_2}). The aim of the controller is to administer the adequate amount of remifentanil to bring and maintain P_{a,CO_2} at the reference, despite pain, disturbances and extreme inter-patient variability in sensibility to the drug. In addition, the controller must fulfill the following clinical constraints to ensure patient safety:

- oxygen saturation (SpO_2) $> 92\%$;
- remifentanil $C_p < 20$ ng/ml and $C_{eff} < 6$ ng/ml;
- controller de/activation possible at all times.

As the P_{a,CO_2} model response to stepwise changes of C_p is linear, of the first-order, a PI controller is our choice. We implement a two degrees-of-freedom PI to be reactive to the error signal while preventing the output to overshoot [9]. The two controller parameters (gain K, integral time T_i) are determined via the area method [9]. In addition to the basic structure, an anti-windup and a safety override system are included. The anti-windup system "turns off" the integral action of the controller whenever the control variable saturates [9]. The override system is included to satisfy the requirements for clinical safety: it allows to switch on/off the controller, it stops/re-starts drug infusion according to the SpO_2 threshold, it ceases drug infusion if the predicted C_p overshoots the threshold, according to an implemented pharmacokinetic (PK) model for remifentanil [10] that relates infusion rate ($\dot{C}_i$) to C_p. The patient simulator comprises two parts: the remifentanil PK model [10], and the New Model. Two signals from the patient simulator are fed to the controller: P_{a,CO_2} and SpO_2.

To test the controller, a controller-driven induction and maintenance of CS is simulated. In order reproduce real-life conditions, inter-patient variability in the sensibility to the drug, generic surgical disturbances (drug interactions, sleep and blood loss) and pain are modelled. Higher and lower drug sensibilities are simulated modifying the PD parameters of remifentanil to obtain a $\pm$ 30% modulation of the pharmacologic effect. Occurrence of a generic surgical disturbance leads to an increase in P_{a,CO_2}, modelled as a sudden + 5 mmHg change. Pain is reported to increase

Drug	k_{e0} [1/min]	EC_{50} [ng/ml]	γ [-]
Fentanyl	0.18	1.04	1.27
Alfentanil	1.15	11.5	1.14
Remifentanil	2.11	0.27	0.88

TABLE I
PD PARAMETERS FOR THE NEW MODEL.

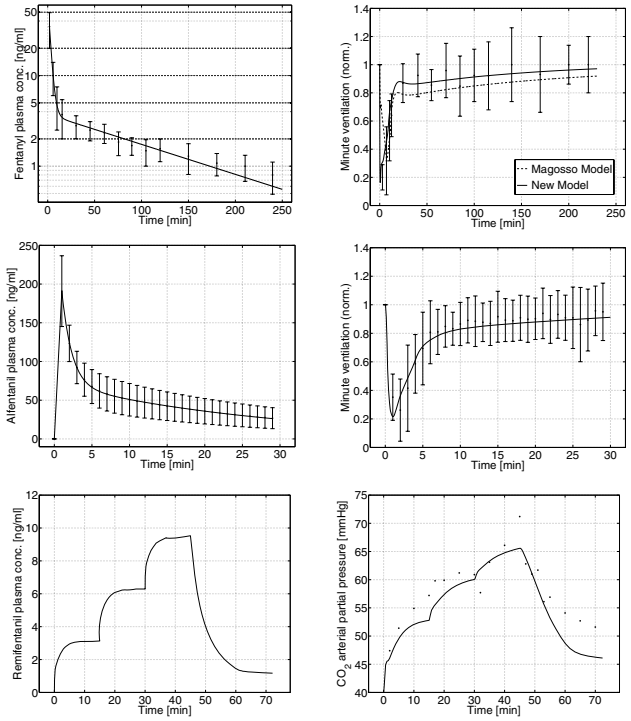

Fig. 3. The New Model. Comparison of model simulations (*continuous line*) with experimental data (*bullets=mean, bar=SD*) for fentanyl (top), alfentanil (middle) and remifentanil (bottom). In the case of fentanyl, the New Model is also compared to the Magosso Model (*dashed line*). Data for remifentanil refer to one volunteer only, as each volunteer received a different infusion profile [4].

ventilation [11]. According to the literature, we model the effect of pain as a decrease of the CO_2 internal reference (P_{b,CO_20}) of Eq. (4) by 5% [12] and as an increase by 10% of the CO_2 production rate [13] in the body, obtaining a steady-state increase of 20% in ventilation after ca. 3 min. The controller is activated at time $t = 10$ min. During the simulation, 10 minutes of painful stimulation and generic surgical disturbance are applied starting at $t = 40$ and $t = 60$ respectively, then removed. No additional oxygen is supplied.

Insensitivity of the controller to parametric changes in the model was established through a series of case studies.

III. RESULTS

Table I reports the estimated PD parameters for the New Model and Figure 3 the fit between the model and the experimental data. In the case of fentanyl, the New Model is also compared to the Magosso Model. The following values are estimated for the controller parameters: $K = 3.35$, $T_i = 2.63$. Figure 4 shows the results of controller testing.

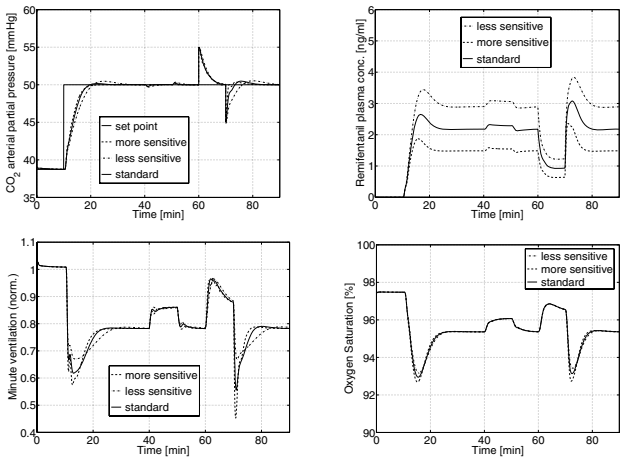

Fig. 4. Controller testing for a standard (*continuous line*), a less sensitive (*dash-dotted line*) and a more sensitive (*dashed line*) patient. From top left, clockwise - CO_2 arterial partial pressure, drug plasma concentration, oxygen saturation, normalized minute ventilation.

Case studies were used to demonstrate that the controller is robust with respect to parametric changes.

IV. Discussion

Drug-induced ventilatory depression represents a well-known side effect of opioids and a major source of morbidity during CS procedures where these drugs are employed. This work introduces a new PD model for drug-induced respiratory depression in humans that overcomes the limitations of the state-of-the-art model in terms of complexity and parameter identifiability. Thanks to its efficient structure, the New Model requires a fewer number of parameters that can be directly estimated from experimental data. The results illustrated in Figure 3 for three widespread opioids confirm that the New Model is able to reliably reproduce measured ventilatory depression for different drugs both following a bolus (fentanyl and alfentanil data) and a continuous infusion (remifentanil data). In particular, in the case of fentanyl, a comparison between the New Model and the Magosso Model shows that the New Model improves the fit with the experimental data, capturing both the steady-state behavior and the fast initial onset of the pharmacologic effect.

Adopting the New Model as a patient simulator, in a further step we explored the possibility of controlling opioid infusion based on transcutaneous CO_2 measurements made recently available by innovative sensors. Simulation results reported in Figure 4 show that the controller succeeds in inducing CS and keeping the target P_{a,CO_2} while rapidly and effectively rejecting pain and surgical disturbances. Maintenance of the target P_{a,CO_2} corresponds to maintenance of sufficient minute ventilation throughout the simulation. The sharp decrease in minute ventilation due to the removal of the surgical disturbance at time $t = 70$ min is almost immediately restored by the controller. Further, the controller individualizes drug administration to the specific patient, administering different amounts of drug according to the individual sensibility. Results in terms of remifentanil plasma concentrations provided by the controller are in accordance with the clinical experience of anesthesiologists at the University Hospital in Bern. The safety override system never had to take action during the infusion, showing that the controller is able to achieve its goals without posing health risks to the patient.

V. Conclusions

This work introduces a new PD model of drug-induced respiratory depression in humans and the innovative concept of controlling drug infusion during CS based on transcutaneous CO_2 measurements. The model shows good agreement with experimental data for different drugs, representing a novel efficient approach to drug-induced ventilatory depression modelling. The controller maintains sufficient ventilation during CS, despite disturbances and accounting for the individual patient sensibility to the drug. The implementation of the controller could improve clinical practice minimizing the incidence of ventilatory depression by tailoring drug infusion to individual needs.

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