Constrained Model Predictive Control of Hypnosis

by

Sara Khosravi

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Abstract

This thesis investigates the design and performance of a model predictive controller (MPC) for the automatic control of hypnosis. It constitutes the first step towards automatic control of anesthesia with constraints on important parameters such as drug concentrations in the body and hemodynamic variables such as blood pressure. The literature suggests, that closed-loop control of anesthesia can significantly reduce drug consumption and lessen recovery times, thus improving the safety and quality of anesthesia care while reducing costs. However, automation of anesthesia is challenging because of shortcomings associated with drug-response modeling, in particular limited data for children and disagreement between published models, inadequate predictive capacity of models owing to inclusion of monitor dynamics in the models, and significant inter/intra patient variability and uncertainty in models. The first part of this thesis introduces a new approach to dose-response modeling and presents models with different clinical end-points for propofol in children and adults. This thesis also presents a new monitor-decoupled model of propofol pharmacodynamics (PD) where the monitor model is clearly excluded from the identified PD. The second part of the thesis concentrates on design of a constrained MPC for hypnosis. While the anesthesia closed-loop concept has already been investigated in the past, there is still a need for a closed-loop control system that explicitly includes robustness in the design step, allows constraints on drug concentrations and physiological parameters, and can incorporate multivariable control of multi drug and multi sensor systems. In this thesis, robust MPC controllers are presented for closed-loop control of depth of hypnosis in adults and children. Robustness in the presence of inter-patient variability is taken into account in the controller design. A novel idea is introduced on how to define and implement physiological constraints in closed-loop control of hypnosis using MPC with a parallel PKPD model. Evaluation of the proposed MPC meets the design specifications and shows that the required robustness against patient uncertainty is achieved and the proposed safety constrained control strategy can potentially reduce the risk of under/over-dosing for most patients by providing controller enforced safety bounds without sacrificing the performance of the closed-loop control system.
Preface

This thesis is based on work conducted in the University of British Columbia, Electrical & Computer Engineering for Medicine (ECEM) group and the Pediatric Anesthesia Research Team (PART) of British Columbia Children’s Hospital under supervision of Dr. Guy Dumont and Dr. Mark Ansermino.

Chapter 2: I was responsible for part of the data collection and the post hoc data analysis, proposing the two-stage pharmacodynamic parameter identification algorithm, identifying the propofol pharmacodynamic models with three different clinical endpoints (the entropy monitor the NeuroSESSE monitor for DOH, and propofol-induced respiratory depression).

Chapter 3: I was responsible for the post hoc clinical data analysis, identifying the entropy monitor dynamics. Performing monitor-decoupled pharmacodynamics identification, time delay estimation, cross validation, covariate analysis, and comparison with the two-stage method.

Chapters 2 and 3 have been published:

Journals:


Chapter 4: I was responsible for identifying the nominal model for the model predictive controller, designing the controller, identifying the uncertainty model and sensitivity functions, perfuming robust stability and nominal performance analysis, and controller tuning.

Chapter 5: I was responsible for part of the data collection and the post hoc data analysis, proposing the design of the constrained model predictive controller, proposing the constraint’s structure, implementing the controller, optimization, and Monte Carlo simulations.

A journal paper based on chapter 4 and 5 is also ready for submission.
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AEP</td>
<td>Auditory Evoked Potential</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
</tr>
<tr>
<td>BIS</td>
<td>Bispectral Index</td>
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<tr>
<td>BP</td>
<td>Blood Pressure</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<tr>
<td>DOH</td>
<td>Depth of Hypnosis</td>
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<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
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<tr>
<td>MISO</td>
<td>Multi Input Single Output</td>
</tr>
<tr>
<td>MIMO</td>
<td>Multi Input Multi Output</td>
</tr>
<tr>
<td>MPC</td>
<td>Model Predictive Control</td>
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<tr>
<td>NMB</td>
<td>Neuro-muscular Blockade</td>
</tr>
<tr>
<td>PID</td>
<td>Proportional–Integral–Derivative</td>
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<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
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<td>PD</td>
<td>Pharmacodynamics</td>
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<tr>
<td>PKPD</td>
<td>Pharmacokinetics Pharmacodynamics</td>
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<tr>
<td>RE</td>
<td>Response Entropy</td>
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<tr>
<td>SBP</td>
<td>Systolic Blood Pressure</td>
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<td>SE</td>
<td>State Entropy</td>
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<tr>
<td>TCI</td>
<td>Target-Controlled Infusion</td>
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<tr>
<td>TV</td>
<td>Tidal-Volume</td>
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Finally to Reza, my better half, thank you for all your love, support, and understanding. I married the best person out there for me, someone I can lean on, someone I can count on... you are my rock!
You can kiss your family good-bye and put miles between you, but at the same time you carry them with your heart, your mind and... Because you do not just live in a world, but a world lives in you.

Frederick Buechner
1. Hypnosis in Anesthesia

1.1 Anesthesia Concepts

In any surgical intervention, anesthesiologists play a very important role before (pre-operative), during (intra-operative), and after (post-operative) surgery. These stages include the assessment of the medical condition and history of the patient before the operation, consultation with the surgical team, providing pain control and life support functions during surgery, supervising care and pain management after surgery, and medically discharging the patient from the recovery room. The main duties of the anesthesiologist during surgery are to administer a combination of anesthesia drugs to induce hypnosis, prevent the awareness of pain, attenuate the body's natural response to injury, and to provide optimal operating conditions for surgeons.

During the surgical procedure, surgical incisions or other stimulating surgical events result in profound changes in the condition of the patient. Therefore, the anesthesiologist must carefully adjust
the anesthesia regime of patients according to their medical condition, response to anesthesia, and requirements of the surgery. Their assessment of the clinical state of the patient relies on their experience and continuous monitoring of vital life functions such as heart rate and rhythm, breathing, blood pressure, blood oxygen level, body temperature and EEG index for depth of hypnosis. Efficient and rapid evaluation of these signs is necessary to avoid over or under dosing of the patient.

Anesthetic drugs are used to blunt the effect of surgical stimulation by blocking the senses. In achieving this, these drugs deny the central nervous system from the information it requires to perform normal body functions such as respiration and blood pressure control. In an under-anesthetized patient, surgical stimulation results in cardiorespiratory changes including an increase in blood-pressure and heart-rate. It can also lead to involuntary movements during the surgical procedure. Another potential risk associated with an under anesthetized patient is intra-operative awareness which can cause post-operative stress, and requiring psychiatric treatment.

Automatic control of anesthesia can assist the anesthesiologist by administering the appropriate drug dosage to keep the patient at an adequate level of anesthesia, reducing the effect of patient variability and providing fast rejection of surgical stimuli [1], [2], [3]. This challenge can be looked at from a control engineering perspective.

1.2 **Pharmacopeia**

To create the state of general anesthesia, anesthesiologists use a combination of hypnotics and analgesics, with or without Neuro-muscular blocking (NMBs) agents.

1.2.1 **Hypnotics**

Hypnotic agents can be categorized into two main categories, inhaled anesthetics and intravenous anesthetics. The major advantage of inhaled anesthetics is that the absorption of drug in blood can be determined by measuring the difference between the inspired and expired concentrations.
since at steady state, the expired concentration correlates with the brain concentration. Intravenous anesthesia has become more popular with the introduction of propofol. Propofol has desirable characteristics which include, smooth induction with suppression of autonomic response, rapid clearance, and fast emergence with decreased nausea and vomiting after recovery [4], [5].

Propofol produces a hypnotic effect through an interaction with the gamma-aminobutyric acid (GABA), a receptor in the central nervous system (CNS). It is possible to estimate the state of hypnosis by monitoring the cortical activity of the patient. As interpretation of the raw electroencephalogram (EEG) requires a trained neurophysiologist for evaluation, many researchers have focused on the development of techniques to analyze EEG patterns to access the state of hypnosis. This has led to the commercialization of a number of EEG-based depth of hypnosis (DOH) monitors [6], [7], [8], [9].

1.2.2 Opioids

Opioids can provoke analgesia without loss of consciousness when administered in small doses. Opioids such as remifentanil and fentanyl are also called anti-nociceptive drugs. They suppress both the signals sent from the nociceptors to the brain and also the signals sent from the brain to the body. Opioids are used during surgery for suppression of response to nociceptive stimulation. The characteristics of remifentanil which are of great interest in anesthesia include rapid onset, noncumulative effect in anesthetized patients and fast recovery. Adequacy of analgesia is usually assessed by monitoring changes in vital signs such as heart rate and blood pressure but more recently specific monitors of nociception suppression have been described [10], [11].

1.2.3 Neuromuscular Blockade

Neuromuscular blockades (NMB) interrupt the transmission of nerve impulse locally around injection site and provide muscle relaxation. They are used in situations such as intra-abdominal surgeries, when anesthesiologists require the blockade of reflex muscle activity in the abdomen. To attain
such a state of paralysis NMBs are used. Certain NMBs such as Succinylcholine have rapid onsets and are more suitable for procedures when short local paralysis is required. NMBS such as rocuronium, are used when a longer lasting paralysis effect is required.

1.2.4 Drug Interactions

When using combinations of different drugs, significant interactions can be observed. A synergic effect means that the resulting effect is greater than what could be expected from the additive effect of two drugs. Drug synergy often appears when using hypnotics in combination with opioids. NMBs do not have any analgesic or hypnotic effects and do not interact in a clinically significant way with those categories of drugs. This synergy reinforces both the effect of the hypnotic and analgesic drug and plays a key role when the drugs are co-administered. Bouillon et al. [12] concluded that the propofol pharmacokinetic model is not affected by remifentanil co-administration. Furthermore, it is stated that the effect of propofol on the remifentanil pharmacokinetic model is only significant when propofol is administered as boluses (bolus, a single dose of a drug). Thus, the synergy is attributed to the pharmacodynamic model and is modeled as a generalization of the Hill function to a surface. Different parameterizations have been suggested for the interaction surface model. The most common one found in the literature is by Minto et al. [13].

1.3 Conduct of Anesthesia

For a patient undergoing general anesthesia, the anesthesia procedure can be divided into three main phases: induction, maintenance and emergence.

- Induction: is the step when the consciousness of the patient transitions from awake to anesthetized. The induction phase of anesthesia usually lasts around 3-5 minutes.
- Maintenance: is the phase of anesthesia that refers to keeping a patient unconscious with or without an analgesic agent. Maintenance can be reached using inhaled volatile agents or continuous infusion of intravenous agents.
• Emergence: phase is achieved by turning off drug delivery machines used at the surgery. This is usually close to the end of surgery (i.e., during skin closure) so that the patient wakes up faster.

1.4 Sensors

A number of techniques have been used to quantify the hypnotic component of anesthesia from the EEG signal. These techniques have resulted in depth of hypnosis monitors that include the Bispectral Index™ (BIS) [6], auditory evoked potential (AEP) [8], M-entropy M-ENTROPY® Monitor [7] and wavelet-based index (WAV$_{CNS}$) from NeuroSENSE [14]. In this study the M-Entropy and NeuroSENSE monitor were considered.

1.4.1 Entropy Monitor

The Entropy monitor (M-ENTROPY® Monitor; GE Healthcare, Finland) measures the degree of entropy (i.e., disorder) in the EEG signal [15]. It is used to gauge the anesthetic effect of an agent (e.g., propofol) on an individual patient. The Entropy monitor provides two indices, the State Entropy (SE) and the Response Entropy (RE). SE is computed between the frequency ranges 0.8-32 Hz which is predominately cortical activity in origin. Alternatively RE includes additional higher frequencies up to 47 Hz reflecting both EEG and muscle activity from the frontalis muscle. A study by Mahon et al. [16] concluded that SE offers potential as a monitor of propofol sedation. The SE is scaled in the range 0-91 and decreases with increasing anesthetic concentration.

1.4.2 NeuroSENSE

The NeuroSENSE monitor was developed specifically for closed-loop control; the dynamic behavior of this monitor is time-invariant and does not add additional computational delays [17]. The WAV$_{CNS}$ index by NeuroSENSE, is expressed in 0-100 scale, see Figure 1.1. Using the NeuroSENSE, optimal hypnosis levels during stable state of general anesthesia are between WAV$_{CNS}$ index of 40-60[18].
1.5 Computer Controlled Drug Delivery in Anesthesia

The idea of automatic control of anesthesia drug delivery dates back to 1950s. But anesthesia automation has only made significant progress in recent years due to advances in the anesthesia field such as development of faster acting drugs and anesthesia sensors that quantify the effect of such drugs. Following are two examples of computer-controlled drug delivery for anesthesia.

1.5.1 Open-Loop Control of Anesthesia

Target-controlled infusion (TCI) is a computerized drug delivery method that is used for a variety of intravenous anesthesia drugs [20]. Although TCI is used widely around the world, the system is not FDA approved. In the TCI of anesthetic drugs, a model-predicted drug concentration in the body (e.g., either blood or effect site) is achieved by targeting a user-defined drug concentration. Since predicted, rather than measured, drug concentrations are targeted, and intra-patient variability cannot be incorporated into the TCI model, there will always be differences between individual predictions of drug concentration and the actual drug concentration achieved. The performance of such an open-loop system is highly dependent on the accuracy of the model on which it is based. These
systems are referred to as open-loop systems, as opposed to closed-loop systems where a control variable is measured and the difference between this value and the set-point is used to change the input rate.

### 1.5.2 Closed-Loop Control of Anesthesia

During closed-loop control of anesthesia, a drug infusion rate is continually adjusted according to feedback obtained from a measurement of clinical effect from the patient. The idea behind closed-loop of anesthesia is not to replace the anesthesiologist, quite the reverse, the objective is to reduce the workload of the anesthesiologist during surgery and to allow the practitioner to concentrate on higher level tasks, to leave room for full attention in case of an emergency, and at all-time provide override of the controller if required. In early 1950s, the work by Bickford et al. [21] showed the potential of closed-loop systems for anesthesia. However in 2015, anesthetic drugs are still delivered manually in most hospitals around the world. This prior art review is limited to studies focused more precisely on the control of hypnosis.

The controller by Struys et al. [1], based on a Hill model acquired during induction and the simple proportional–integral–derivative (PID) controller by Absalom et al. [22] were both designed to calculate the required propofol concentration changes at the effect-site. A TCI system was employed to achieve these changes. But due to the empirical tuning of the controller, the performance varied significantly between patients with oscillatory behavior in some cases.

Gentilini et al. [23], designed an Internal Model Control system with the hypnotic gas isoflurane to control the mean arterial blood pressure (sensitive to noxious stimuli) and the BIS. An advantage of this system is that the drug plasma concentration of inhalational gases such as isoflurane is closely related to the end-tidal expired gas concentration which can be conveniently measured. This is in contrast to use of intravenous agents for which measurement of drug concentration is impractical. Anesthesia in the 40 patients in this clinical study was manually induced with the controller taking over only for the maintenance phase.
Puri et al. [24] compared an adaptive PID controller with manual control in a clinical trial (40 patients) with the BIS as clinical end-point, maintaining similar hemodynamic stability as in manual control. The controller is heuristically tuned and the study does not provide detailed description of the control algorithms.

A model-predictive controller-based system for control of depth of hypnosis has been described by Sawaguchi et al. [25]. The controller which further includes a set of rule-based fallback procedures was clinically tested on 79 patients. Induction of anesthesia was manually controlled and the measured response was used to identify model parameters for the individualized MPC controller.

Liu et al. [26] first introduced a rule-based controller somewhat similar to a PID controller. The empirically tuned controller was compared with manual control during a randomized controlled trial with 164 patients. The system was reported to outperform manual control. Later Liu et al. [27] presented a dual loop controller that manipulates both the propofol and remifentanil infusion rates based on the BIS index alone. The controller that manipulates the remifentanil infusion rate combines a proportional action with a number of heuristic rules. Randomized clinical trials involving 167 patients during a wide variety of procedures showed that the system provides better control of the BIS index than manual control. This system, similar to the first system introduced by authors, manually induces the patient by setting effect-site concentrations targets for both propofol and remifentanil.

The main difficulty in the design of controllers for closed-loop control of anesthesia is the significant intra- and inter-patient variability that is observed in response to a standard dose of drug [4]. This has led to concerns about the safety of closed-loop control systems in anesthesia. To reach acceptance for a closed-loop drug delivery from clinicians and regulatory authorities, the control system will require a certification procedure likely to include stability and robust performance criteria. The group at Electrical and Computer Engineering in Medicine in University of British Columbia has been focused on designing a robust controller for automatic control of anesthesia for the past 10 years. Dumont et al. described a rigorous approach to robust PID tuning for 44 adult patients [3]. The approach was later incorporated in a feasibility study in adults using the NeuroSENSE monitor where
results showed the controller provided clinically adequate anesthesia with achieving fast induction (median time to induction of 4 minutes), the control variable within the target range 88% of the times. A similar system was also developed for children and resulted in a pilot study reported in Soltesz et al. [28], van Heusden et al. [29], and West et al. [30]. Anesthesia was closed-loop controlled in 102 children in this study using the NeuroSENSE monitors as a measure of clinical end-point. Clinical evaluation of the system showed that closed-loop control in children is feasible and a robustly tuned PID controller can accommodate the inter-patient variability in children. Our research group has also been working on a multi input multi output (MISO) mid-ranging controller designed for the control of depth of hypnosis, based on the co-administration of both propofol and remifentanil. This is achieved by splitting the control error into a high frequency part, used to control the fast actuator (remifentanil), and a low frequency part, used to control the slow actuator (propofol). A clinical study is still ongoing.

The system used is shown in Figure 1.2 in a clinical setting.

1.6 Goals

The objective of this thesis is to design and evaluate the performance of a robust closed-loop controller for the hypnosis state of anesthesia using a depth of hypnosis index as a control variable.
The aim is to provide a drug regime for the administration of propofol, depending on the targeted depth of hypnosis, to avoid under or over dosing. There are three main design criteria for the controller:

1) The basis for a rigorous design is a description of the variability of the dose–response characteristics of the patients within the study population, to be used in the controller design. The controller must be robust with respect to model uncertainty to compensate for the intra- and inter-patient variability during induction and maintenance of anesthesia.

2) A closed-loop control system for anesthesia necessitates safety constraints on estimated drug concentrations and magnitude of infusion rates. The constraints can be due to the physical hard
constraints on the system or may be defined based on the therapeutic window of the anesthesia drug [31].

3) Controlling anesthesia, as the ultimate goal, entails the control of both hypnosis and analgesia with safety constraints incorporated in the controller design. The controller should allow for multivariable control.

Model predictive control is an optimization-based approach, which is able to handle multivariable control problems and to allow constraints to be imposed on both the controlled and manipulated variables. MPC is the controller of choice for this thesis.

1.7 Thesis Organization

Chapter 2: This chapter describes the pharmacokinetic (PK) and pharmacodynamics (PD) pharmacology models that together describe the complete dose and response of a drug. This chapter also presents a new approach to PD modeling, and also introduces two PD models with different clinical end-points for propofol. It further compares the identified PD parameters with the presented approach to PD parameters identified with different techniques. Results are discussed in at the end.

Chapter 3: This chapter describes the advantages of decoupling monitor dynamics from PD parameters during the identification process. Dynamics associated with the depth of hypnosis monitor, M-Entropy Monitor are characterized. Furthermore, a detailed discussion of a monitor-decoupled approach to PD modeling is presented and results are discussed in details.

Chapter 4: In this chapter a model predictive controller that includes robustness in the design step is presented for adults and children assuming that no constraints are active. It also describes the controller design, including definition of a nominal model, the sensitivity functions and the requirements to achieve robust stability and nominal performance. Furthermore, robust tuning of the controller and statistical analysis and results of the controllers are presented in presented in this chapter.
Chapter 5: This chapter describes safety constraints in closed-loop control of hypnosis and their necessity. A Monte Carlo simulation algorithm is presented and Monte Carlo simulations are used to observe the robustness. Simulation results of the constrained MPC compared with the previous unconstrained MPC are also reported.

Chapter 6: Concluding remarks and outlook on future work are given in Chapter 6.
2. Modeling Anesthetic Drugs

Characterization of the patient model and its uncertainty is essential for designing a closed-loop control of drug delivery system. In the context of this work the patient model is defined as the relationship between propofol dose and its measured effect on the patient. Such models are typically derived from an understanding of PK and PD. PK describes the absorption, distribution, metabolism and excretion of administered drugs (i.e., what the body does to the drug). PD describes the responsiveness of receptors to drugs and the mechanism by which these effects occur (i.e., what the drug does to the body). Receptors are the components of the cell that interact with drugs to initiate a sequence of events leading to pharmacologic effect.

Knowledge of the PK and PD of intravenous drugs defines the dose-response relationship of a drug. Combining these models can offer a continuous prediction of drug concentration (both in blood and at the clinical effect site) and the predicted clinical effect. In the field of anesthesia, many PK and PD studies have investigated the effect of the anesthetic agent propofol in both adults [32] and children [33] [34] [35], using a variety of clinical effects.
This chapter is organized as follows. Section 2.1 describes the PK and PD models in terms of mathematical expressions. Section 2.2 states the current issues with available models. Section 2.3 presents a new approach to PD modeling, plus two PD models with different clinical end-points for propofol. Section 2.4 compares the identified PD parameters with the presented approach to PD parameters identified with different techniques. Results are discussed in Section 2.5.

2.1 Pharmacology Principles and Concepts

2.1.1 Pharmacokinetics

A pharmacokinetic model of a drug is a mathematical expression relating the drug blood plasma concentration $C_p(t)$ to the administered dose $I(t)$:

$$PK(s) = \frac{C_p(s)}{I(s)}.$$  

The PK model is used to predict the blood concentration profile of a drug in response to drug administration. It consists of a series of hypothetical compartments representing theoretical body tissues and organs as well as the central blood volume. The drug flows into each compartment, either from external anesthetic administration or via transfer from another compartment. Drug flows out of the compartment by elimination through metabolic clearance or by transfer to other compartments. A block diagram of a 3-compartmental PK model is shown in Figure 2.1.

The Marsh PK model [33] and the Schnider PK model [36] for propofol, were proposed for adults and have been in use since the 1990s. In 2000, Schüttler and Ihmsen carried out an extensive propofol adult PK study covering 270 individuals where they also quantified the influence of covariates such as age, lean body mass and gender[37]. Paedfusor [38] and Kataria, [39] are the most commonly pediatric PK models used by anesthesiologists. The Paedfusor PK model and the Marsh PK model have been incorporated in a pediatric and adult TCI pump respectively.
The mathematical expression for the 3-compartmental PK model by Schüttler and Ihmsen is expressed here in a state-space representation:

\[
\begin{bmatrix}
\dot{C}_1 \\
C_2 \\
C_3
\end{bmatrix} = \begin{bmatrix}
-(k_{10} + k_{12} + k_{13}) & k_{21} & k_{31} \\
k_{12} & -k_{21} & 0 \\
k_{13} & 0 & -k_{31}
\end{bmatrix} \begin{bmatrix}
C_1 \\
C_2 \\
C_3
\end{bmatrix} + \begin{bmatrix}
1/V_1 \\
0 \\
0
\end{bmatrix} \cdot u(t)
\]

\[
C_p(t) = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix} \begin{bmatrix}
C_1 \\
C_2 \\
C_3
\end{bmatrix},
\]  \hspace{1cm} (2.2)

where, \( C_1 \) is the concentration in central compartment and \( C_2 \) and \( C_3 \) are the concentrations in the peripheral compartments, \( k_{10} \) is the central compartment elimination rate constant and \( k_{12}, k_{13}, k_{21} \) and \( k_{31} \) are the inter-compartmental rate constants and \( V_1 \) is the central compartment volume [37].

![Figure 2.1: a 3-compartmental pharmacokinetic model.](image)

Table 2.1 presents the PK parameters for two popular adult models, Marsh PK model and Schnider PK mode. Table 2.2 presents the PK parameters for two most commonly used pediatric models, Paedfsus and Kataria.
Modeling Anesthetic Drugs

<table>
<thead>
<tr>
<th></th>
<th>Marsh</th>
<th>Schnider</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_1$ (L/kg)</td>
<td>0.228</td>
<td>4.27 L</td>
</tr>
<tr>
<td>$V_2$ (L/kg)</td>
<td>0.463</td>
<td>18.9-0.391 x (age-53) (L)</td>
</tr>
<tr>
<td>$V_3$ (L/kg)</td>
<td>2.893</td>
<td>238 (L)</td>
</tr>
</tbody>
</table>

| $K_{10}$ (min$^{-1}$) | 0.119 | $0.443 + 0.0107 x (weight -77) – 0.0159 x (LBM-59)+0.0062 x (height-177)$ |
| $K_{12}$ (min$^{-1}$) | 0.112 | 0.302-0.0056 x (age-53) |
| $K_{13}$ (min$^{-1}$) | 0.042 | 0.196 |
| $K_{21}$ (min$^{-1}$) | 0.055 | $[1.29-0.024 x (age-53)]/[18.9-0.391 x (age-53)]$ |
| $K_{31}$ (min$^{-1}$) | 0.0033 | 0.0035 |

Table 2.1: PK parameters for two popular adult models, Marsh PK model [33] and Schnider PK model [36].

<table>
<thead>
<tr>
<th></th>
<th>Paedfusor</th>
<th>Kataria</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_1$ (L/kg)</td>
<td>0.458</td>
<td>0.52</td>
</tr>
<tr>
<td>$V_2$ (L/kg)</td>
<td>1.34</td>
<td>1.0</td>
</tr>
<tr>
<td>$V_3$ (L/kg)</td>
<td>8.20</td>
<td>8.2</td>
</tr>
<tr>
<td>$K_{10}$ (min$^{-1}$)</td>
<td>70 x weight$^{0.3}/458.4$</td>
<td>0.066</td>
</tr>
<tr>
<td>$K_{12}$ (min$^{-1}$)</td>
<td>0.12</td>
<td>0.133</td>
</tr>
<tr>
<td>$K_{13}$ (min$^{-1}$)</td>
<td>0.034</td>
<td>0.051</td>
</tr>
<tr>
<td>$K_{21}$ (min$^{-1}$)</td>
<td>0.041</td>
<td>0.059</td>
</tr>
<tr>
<td>$K_{31}$ (min$^{-1}$)</td>
<td>0.0019</td>
<td>0.0032</td>
</tr>
</tbody>
</table>

Table 2.2: PK parameters for two popular pediatric models, Paedfusor PK model [38] and Kataria PK model [39].
2.1.2 Pharmacodynamics

A pharmacodynamics model mathematically expresses the observed effect of a drug, $E(s)$ as a function of its plasma concentration:

$$PD(s) = \frac{E(s)}{C_p(s)} . \quad (2.3)$$

The characteristic of any drug, propofol for the purpose of this study, can be expressed by its dose-response curve, see Figure 2.2. This characteristic is usually described using the Hill equation as follow:

$$E(t) = E_0 \left[1 - \frac{C_p^{\gamma}}{EC_{50}^{\gamma} + C_p^{\gamma}}\right], \quad (2.4)$$

where, $E(t)$ and $E_0$ are the instantaneous and the baseline effects, respectively, $C_p$ is the steady-state plasma concentration, $EC_{50}$ is the steady-state propofol concentration associated with 50% of the full clinical effect, and $\gamma$ is the cooperativity coefficient describing the steepness of effect.

![Figure 2.2: Dose-response model](image)
PK and PD studies have shown that, the concentration at the effect-site lags the plasma drug concentration. To incorporate this characteristic into the dose/response model, an additional compartment to the conventional PK models was proposed by Sheiner et al. [40]. The new PK model (four compartment PK model) included an effect compartment connected to the central compartment where a rate constant $k_{eo}$ expresses the dynamics of transfer of the plasma concentration to the effect-site. Therefore, it is possible to mathematically express the effect-site drug concentration $C_e(s)$ as a function of the $C_p(s)$.

$$C_e(s) = \frac{k_{eo}}{s + k_{eo}} \cdot C_p(s). \quad (2.5)$$

The relationship between the drug concentration at the effect-site and the actual clinical effect can be modeled using the Hill equation by modifying (2.4) such as follows:

$$E(t) = E_0 \left[ 1 - \frac{C_e'(t)}{EC_{50} + C_e'(t)} \right]. \quad (2.6)$$

Figure 2.3 shows the propofol infusion profile and predicted propofol concentrations in a 4-compartment PK model for a TCI simulation. The simulation is based on a Paedfusor PK model for a 20kg patient. The target for propofol concentration is set to 4µg/ml.

### 2.1.3 Dose-Response Model

The complete drug-response relationship of propofol can be expressed by combining the PK and PD models [4]. The PK model in (2.2) can be rewritten as a zero-pole-gain transfer function:

$$PK(s) = K_{pk} \frac{(s + z_1)(s + z_2)}{(s + p_1)(s + p_2)(s + p_3)}, \quad (2.7)$$

where $K_{pk}$ is a constant gain, and $p$ and $z$ represent the poles and zeros, respectively.
Figure 2.3: TCI Simulation results of Paedfusor 4 compartments PK model for a 20kg pediatric patient when the target propofol concentration is set to 4µg/ml.
The linearized PD model for induction phase of anesthesia is calculated as:

$$PD(s) = e^{-T_{p1} s} \frac{k_d}{s + k_d} \cdot \frac{1}{2 \cdot EC_{50}}.$$  \hspace{1cm} (2.8)

The linearized PKPD model is obtained by combining the PK and PD: (2.7), (2.8).

$$PKPD(s) = e^{-T_{p1} s} K \frac{(s + z_1)(s + z_2)}{(s + p_1)(s + p_2)(s + p_3)(s + p_4)},$$  \hspace{1cm} (2.9)

where $K$ is the overall PKPD(s) gain.

2.1.4 Time-to-Peak-Effect

The time-to-peak-effect ($T_{peak}$) is a clinically important index that can be derived from the PKPD model [41]. It estimates the time required for propofol to achieve its maximal effect after its ideal impulse-like administration. Using the PK model and $k_{e0}$ identified as part of the PD model, $T_{peak}$ is calculated by: 1) calculating $C_p$ as the impulse response of the PK model; 2) calculating $C_e$ using (2.5); and 3) calculating the time when $C_e$ reaches its maximum concentration.

2.2 Patient Model Identification

2.2.1 Challenges in Identifying Patient Models

One of the challenges in the development of a closed-loop system for automatic control of hypnosis with propofol is the identification of reliable patient models and characterizing the uncertainty associated with them. Pharmacokinetic models proposed in the literature are consistent and have received acceptance from the clinical community. For example, PK models as mentioned in Section 2.1.1 are included in commercial TCI systems. The situation is very different with PD models. There is limited availability of PD models especially for children and there is also a clear need to improve the performance of the existing PD models. Because of this, the pediatric PK models that are used for propofol TCI are frequently calculated with $k_{e0}$ obtained from adult studies.
to provide an estimate of effect-site concentration. But PD differences between adults and children dictate that it is unacceptable to extrapolate the adult value of $k_{e0}$ to pediatric PK models. Also the PD models that are derived specially for use with one particular monitor/sensor cannot be readily used to predict the time course of an effect measured by a different monitor/sensor. A problem with many PD models in literature is that in developing them, the dynamic and nonlinear behavior of the sensor/monitors is not explicitly considered. Therefore the resulting PD model implicitly includes the dynamics of sensor/monitors.

To investigate and address some of these issues, we proposed and investigated a new and easy method for identifying PD models from clinical data and applied the method to clinical data. We compared the identified model parameters with those available in the literature and also examined the appropriateness of the method of PD identification for control design. The remainder of this chapter presents the details and results of PD identification. The concerns with decoupling of monitor dynamics from the PD models during identification step and quantification of uncertainty with respect to patient model are addressed in later chapters.

### 2.2.2 Two-Stage Approach to PD Identification

We introduced and investigated the two-stage approach as an alternative approach to the traditional method of characterizing the pharmacodynamics of propofol anesthesia [42]. In the two-stage approach, for each individual, the PD model was identified using an exhaustive search of $k_{e0}$ combined with constrained least-squares estimation of $EC_{50}$ and $\gamma$. To prevent non-physiologic PD parameters, the model identification was limited to the following parameter space: $1e^{-2} < k_{e0} < 2e^0$, $1e^{-1} < \gamma < 1e^1$, and $0.1 \times \text{max}(C_p) < EC_{50} < 0.9 \times \text{max}(C_p)$, where $\text{max}(C_p)$ is the maximum value of the predicted plasma propofol concentration for an individual subject. For each $k_{e0}$ in the search space, the values of $EC_{50}$ and $\gamma$ that would minimize the mean-squared error between measured $E(t)$ and predicted $\hat{E}(t)$ output were identified.
2.3 Introducing New Pharmacodynamic Models

2.3.1 Study 1: Pediatric PD Model With Entropy Monitor

Previous pediatric PD studies investigating propofol administration in children have described PD models based on the effect of propofol on EEG as measured by monitors, BIS and AEP [15], [6], [8]. In contrast, a PD study based on the Entropy monitor has not been reported. For validating the two-stage approach, data reported in a previously published clinical study with Entropy Monitor was utilized [43].

Experimental Protocol:

Dosani et al [43], obtained written informed consent for 52 children who were scheduled for elective upper or lower gastrointestinal endoscopic investigation at British Columbia’s Children’s Hospital in Vancouver, British Columbia, Canada (Ethics Certificate H07-01159). These children had an American Society of Anesthesiologists (ASA$^1$) status of I or II. The mean (standard deviation) age and weight were 11(2.4) yr and 43(15) kg respectively, see Table 2.3.

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>12</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>44</td>
<td>20.8</td>
<td>79.3</td>
</tr>
</tbody>
</table>

Table 2.3: Demographics of the Pediatric Population (n=38), Fourteen patients were excluded from further analysis due to inadequate entropy measurements.

A self-adhesive Entropy™ sensor was applied to the forehead of the patient prior to the induction of anesthesia. Connected to the Entropy monitor, this measured the SE. Propofol 1% was administered intravenously at a loading dose of 4mg/kg using a standard infusion pump (Medex Protégé® 3010 Medex-A Furon; Healthcare Company, USA). Infusion rates ranged from 1000 mcg/kg/min to 2300 mcg/kg/min, and were determined for each subject by a randomization schedule.

---

$^1$ American Society of Anesthesiologists physical status classification system. ASA I: normal healthy patient, ASA II: patient with mild systemic disease.
in the related study [43]. Once the loading dose of propofol had been delivered, the infusion rate was maintained at 200mcg/kg/min for four minutes. During our analysis of data, 21 subjects were excluded from further analysis: 3 due to failure to mark the time at which the loading dose of propofol was initiated; 16 due to missing or corrupted SE measurement data due to movement or inadequately applied sensor in the awake child; 2 due to missing induction phase data.

Model Identification:

The Paedfusor [38] and Kataria [39] PK models were used to predict the plasma concentration profile of propofol in response to its administration. Given the predicted plasma propofol concentrations, the effect-site propofol concentration was calculated by equation (2.5). The relationship between the propofol concentration at the effect-site and the actual clinical effect, SE index from the M-Entropy monitor, was modeled using the standard Hill equation (2.6). Using the predicted plasma propofol concentration and the SE measurements of each individual, the PD model was identified with a combined linear-nonlinear regression analysis, two-stage approach for both the Paedfusor and Kataria PK models.

Results and Discussions:

The identified PD model parameters are summarized in Table 2.4. The value of $k_{e0}$ derived in this study was significantly higher than those previously reported for pediatric PD models for propofol using different EEG monitors. For both Paedfusor and Kataria models, the population mean value for $k_{e0}$ obtained using SE as the clinical end-point (3.0min⁻¹ and 1.4 min⁻¹) were larger (faster) than values reported for BIS in a previous study (0.91min⁻¹ and 0.41min⁻¹) [35]. This suggests that $k_{e0}$ estimated using BIS is not acceptable for use with the SE monitor. Other than the different processing characteristics of the different monitors used in these investigations, differences in study populations may also explain, in part, these differences in $k_{e0}$ values.
Modeling Anesthetic Drugs

<table>
<thead>
<tr>
<th>PK Model</th>
<th>( k_{e0} ) [min(^{-1})]</th>
<th>( EC_{50} ) [mcg/ml]</th>
<th>( \gamma )</th>
<th>( T_{peak} ) [s]</th>
<th>MSE [e(^{-3})]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paedfusor</td>
<td>3.0±1.9</td>
<td>4.7±0.8</td>
<td>5.2±1.4</td>
<td>66.0±23.5</td>
<td>5.4±2.8</td>
</tr>
<tr>
<td>Kataria</td>
<td>1.4±0.8</td>
<td>3.5±0.6</td>
<td>4.3±1.3</td>
<td>85.9±18.7</td>
<td>6.1±3.0</td>
</tr>
</tbody>
</table>

Table 2.4: Identified PD model parameters based on two-stage PD modeling with Entropy as clinical-endpoint [42].

<table>
<thead>
<tr>
<th>Two-stage Approach (mean+/−SD)</th>
<th>Mixed Effects Model Typical Value (standard error), SD(η)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k_{e0} )</td>
<td>2.38±0.6</td>
</tr>
<tr>
<td>( \gamma )</td>
<td>5.29±1.7</td>
</tr>
<tr>
<td>( EC_{50} )</td>
<td>4.73±0.8</td>
</tr>
</tbody>
</table>

Table 2.5: Two-Stage versus Mixed Effects Approach [44], [45] to Pharmacodynamic Modeling of Propofol in Children Using State Entropy. Identified PD Parameters (SD: Standard Deviation, Standard Error).

For comparison, the PD models identified using the two-stage approach were compared with a mixed-effect modeling approach [46]. In the mixed-effects approach, each PD parameter was assumed to consist of fixed and random components. Initial conditions in the neighborhood of the PD parameter values of the two-stage PD model were used to derive the mixed-effects model and the first-order conditional estimation method was used to identify the PD parameters. The results of the two-stage versus Mixed-effects approach to pediatric PD identification using State Entropy are presented in Table 2.5. The Two-stage and mixed-effects approach resulted in a \( k_{e0} \) of 2.38 min\(^{-1}\) and 2.66 min\(^{-1}\), \( EC_{50} \) of 4.73mcg/ml and 4.84mcg/ml, and \( \gamma \) of 5.29 and 5.68, respectively. The bootstrap estimates in terms of mean (SD) of the PD parameters were \( k_{e0} \) of 2.38 (0.10), \( \gamma \) of 5.30 (0.30), and \( EC_{50} \) of 4.73 (0.14).
2.3.2 Study 2: Pediatric PD Model With Propofol Induced Respiratory Depression

PD models of a drug are not unique in that they only describe one of the many different possible clinical end-points of a drug. Another effect of propofol is on ventilation. Propofol results in a dose dependent depression of ventilation that may lead to hypoxemia\(^2\) requiring artificial ventilation [47]. Unless appropriately managed, this situation can lead to disturbing complications such as permanent brain injury. An improved understanding of the PD models of propofol induced respiratory depression can be useful in administering the propofol and maintaining spontaneous breathing in patients. Dosani et al. [43] showed that the clinically observed respiratory depression is dependent on both the propofol concentration in the brain and its rate of rise. The following study investigated using the easily available ventilation data as clinical end-point for PD identification.

Experimental Protocol:

Data reported in a previously published clinical study and outlined in 2.3.1 was utilized. Respiratory monitoring (M-CAiOVX module, Datex-Ohmeda, Finland) was performed for a minimum of 3 minutes in prior to the induction of anesthesia during tidal breathing using a fractional inspired oxygen concentration of 0.21 at 61/min through the anesthetic circle system. An adequate mask seal was accepted if the CO\(_2\) monitor generated a square waveform and a difference of less than 5% was observed between the measured inspiratory and expiratory volumes. The rate of infusion for each subject was determined by a randomization schedule which aimed to optimize the rate of administration to maintain spontaneous breathing [43]. Fresh gas was maintained at 6l/min throughout the induction phase with the FiO\(_2\) increased to 0.5. Respiratory parameters including tidal-volume (TV)\(^3\), minute volume\(^4\), respiratory rate\(^5\), and end-tidal CO\(_2\)\(^6\) were recorded every 5s.

---
\(^2\) Hypoxemia is an abnormally low level of oxygen in the blood.
\(^3\) Tidal-volume is the lung volume representing the normal volume of air displaced between normal inhalation and exhalation when extra effort is not applied.
\(^4\) Minute ventilation is the volume of gas inhaled or exhaled from a person's lungs per minute.
\(^5\) Respiratory rate is the number of breaths taken within a set amount of time (typically 60 seconds).
\(^6\) End-tidal CO\(_2\) is the level of carbon dioxide released at the end of expiration.
Model Identification:

The Paedfusor and Kataria PK models were used to predict the propofol plasma concentration, and the PD models for tidal-volume, respiratory rate and end-tidal CO₂, comprising of an effect-site equilibration rate constant and the Hill equation, were identified using the two-stage method. In this model EC₅₀ describes the propofol concentration that causes 50% depression of tidal volume during spontaneous breathing.

Results and Discussions:

In contrast to tidal volume, respiratory rate and end-tidal CO₂ did not show clear dependence on the predicted plasma concentration and were not considered as clinical-end point of interest for PD modeling of propofol. The PD models for tidal volume with Paedfusor and Kataria PK models are presented in Table 2.6. The values of kₑ₀ estimated for SE in Study 1 were larger than those for TV, suggesting that the respiratory depressant response is slower than the EEG response. Similarly, the values of γ estimated for SE were larger than those for TV, suggesting that the emergence of, and recovery from, the EEG response may exhibit a narrower physiologic effect (smaller range of response) compared to its respiratory counterparts once the drug concentration reaches a certain threshold.

Mixed-effects approach to PD modeling was also followed as explained in Study 1 with TV as clinical end-point. The identified PD models for tidal volume derived from two-stage and mixed-effects modeling approaches are summarized in Table 2.7. The typical values identified from each of two-stage and mixed-effects approaches yielded kₑ₀ of 1.06 min⁻¹ and 0.72 min⁻¹; EC₅₀ of 3.18 and 3.00 mcg/ml; γ of 1.10 and 0.93. The results were also compared with a Pooled PD identification approach using of Propofol-Induced tidal-volume depression [45]. The optimal population PD parameters were identified in a single step by grouping together all the available patient data. In this approach kₑ₀ identification was limited to 1e⁻²<kₑ₀<2.0e⁰ but no additional constraints were considered on EC₅₀ and γ. The pooled approach resulted in a kₑ₀ of 1.24 min⁻¹; EC₅₀ of 3.44 mcg/ml; and γ of 0.83. The typical
PD parameters $k_{e0}$, EC$_{50}$ and $\gamma$, with clinical end-point of tidal-volume, derived from two-stage, mixed-effects, and pooled modeling are presented in Table 2.6 and Table 2.7. The results show, that PD parameters identified with different approaches are comparable.

<table>
<thead>
<tr>
<th></th>
<th>$k_{e0}$ [min$^{-1}$]</th>
<th>EC$_{50}$ [µg/ml]</th>
<th>$\gamma$</th>
<th>T$_{PEAK}$ [s]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paedfusor</td>
<td>1.1±0.8</td>
<td>3.2±2.1</td>
<td>1.1±1.0</td>
<td>188±142</td>
</tr>
<tr>
<td>Kataria</td>
<td>1.0±0.7</td>
<td>2.8±1.9</td>
<td>1.2±0.9</td>
<td>157±111</td>
</tr>
</tbody>
</table>

Table 2.6: Identified PD model parameters based on two-stage PD modeling with tidal-volume as clinical-endpoint.

<table>
<thead>
<tr>
<th></th>
<th>Two-Stage Approach (mean+/-SD)</th>
<th>Mixed Effects Model Typical Value (standard error), SD($\eta$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{e0}$ [min$^{-1}$]</td>
<td>1.01±0.8</td>
<td>0.72(SE 0.45), SD($\eta_1$)=7.9e$^{-6}$</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>1.1±1.0</td>
<td>0.93 (SE 0.20), SD($\eta_2$)=0.06</td>
</tr>
<tr>
<td>EC$_{50}$ [µg/ml]</td>
<td>3.3±2.1</td>
<td>3.00 (SE 0.79), SD($\eta_3$)=0.04</td>
</tr>
</tbody>
</table>

Table 2.7: Two-Stage versus Mixed Effects Approach [46] to Pharmacodynamic Modeling of Propofol in Children Using of Propofol-Induced Tidal Volume Depression. Identified PD Parameters (SD: Standard Deviation, Standard Error).

### 2.3.3 Study 3: Pediatric PD Model With NeuroSENSE Monitor

Pharmacodynamics and Pharmacokinetics models are traditionally used to model the effect of intravenous anesthetic drugs. However, a physiologically meaningful set of PD parameters is not required for controller design and is not essential for prediction of closed-loop performance provided that the experimental conditions for identification and closed-loop control are similar[48]. In this study, a set of models describing the effect of propofol in children with NeuroSENSE is identified specifically for the design of a robust linear closed-loop controller.
Experimental Protocol:

Following approval of the institutional ethics board, data was analyzed for 30 children, ASA category I/II undergoing elective general surgery using total intravenous anesthesia (TIVA). The WAV\textsubscript{CNS} index as measure of the depth of hypnosis was recorded during induction and maintenance of anesthesia. Corresponding propofol infusion rates were recorded manually. Sixteen recordings were discarded due to corrupted data (6), missing data (8) or a strong reaction to tracheal intubation (2) as reflected in the measure of depth of hypnosis. Data for the first 8 min following the start of the propofol infusion were used for model identification. The Paedfusor PK model was used to predict the propofol plasma concentration.

Model Identification:

Three different methods were employed for model identification for control. The block diagrams of these models are presented in Figure 2.4.

**Two-stage Plus Delay PD model:** The PD model was identified using an extensive search of $k_\infty$ and time-delay combined with constrained least-squares estimation of $\gamma$ and $EC_{50}$.

**Bibian’s PD model:** In the first step, the linear part of the PD model plus time-delay was identified. In the next step, a search algorithm determined the hill parameter that minimizes the root mean squared of the residual[4];

**Black-box model:** Parameters of a first-order time-delayed model, directly relating the infusion profile to clinical effect were identified.

Closed-loop performance of a robust linear controller, designed based on the Black-box model, was verified for the three model sets.

Results and Discussions:

Figure 2.5 compares the results of the three model identification approaches for a particular patient. The results show that similar data fits were obtained with the three different models. The results in Table 2.8 show that these fits were achieved with different parameter combinations. These
results further reveal the limited excitation in the signals used for identification. Data from induction of anesthesia is not sufficiently exciting to identify the non-linearity, the time delay and the time constant. The predicted mean (SD) for EC\textsubscript{50} and \( \gamma \) were 4.5(1.4) and 5.5(1.8) \( \mu \text{g/ml} \) and 2.1(0.8) and 1.7(0.2) for the two-stage plus delay PD model and the Bibian’s PD model, respectively. The Bibian’s PD model contained a significantly larger delay 31(24) seconds, compared with the two-stage plus delay PD model 14(20) seconds.

Figure 2.4: The block diagram of (a) The two-stage plus delay and Bibian’s PD model (b) The Black-box PD model, where U is the infusion rate, \( T_p \) is the time constant and the DOH is depth of hypnosis index.
Figure 2.5: Patient model identification for subject 14 (top) and subject 19 (bottom). (Green: Black-box model, Blue: Two-stage Plus Delay model, Red: Single-step model).

<table>
<thead>
<tr>
<th>PD Model</th>
<th>$K_d$ [min$^{-1}$]</th>
<th>$EC_{50}$ [mcg/ml]</th>
<th>$\gamma$</th>
<th>Delay [s]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two-stage plus delay</td>
<td>1.94 (1.58)</td>
<td>4.63 (1.47)</td>
<td>2.01 (0)</td>
<td>17.71 (21.31)</td>
</tr>
<tr>
<td>Bibian’s</td>
<td>6.53 (12.78)</td>
<td>5.61 (1.89)</td>
<td>1.70 (0)</td>
<td>32.50 (26.07)</td>
</tr>
</tbody>
</table>

Table 2.8: Identified PD model parameters based on Two-stage Plus Delay and Bibian’s PD modeling with $WAV_{CNS}$, as clinical-endpoint [49].

Predicted closed-loop performance with a robust linear controller was similar for all three model sets, despite the parametric or structural differences, see Figure 2.6. Clinical evaluation of the controllers in a pilot study confirms the reliability of the models for the design of linear controllers [50].
2.4 Discussion

This chapter introduced the concepts of pharmacokinetic and pharmacodynamic models and their mathematical representations. It further presented and compared PD models that describe the anesthetic effect of propofol in children age 6-16 years for State-Entropy Index, SE, and respiratory tidal volume as clinical end-points. A pediatric PD model for propofol was also identified with WAV\textsubscript{CNS} and was compared with two models identified for the design of a robust linear closed-loop controller.

The two-stage approach was introduced for PD parameter identification and the approach was compared with frequently used mixed-effect modeling and pooled modeling approach. Comparable
results obtained by these approaches suggest that because of its comparative computational efficiency in dealing with large amount of data, the two-stage approach may serve as an attractive alternative to the mixed-effects approach in situations where large amount of PKPD data are available.

Pharmacodynamic Model identification from clinical data was challenging and identifiability issues regarding the nonlinear model structure are demonstrated by the spread of PKPD model parameters that achieve similar model fits for the identification data. The data from closed-loop induction is not sufficiently exciting to consistently identify the parameters of a PKPD model structure, and consequently the identified parameters are of limited physiological significance. Also propofol is often used in combination with an opioid such as remifentanil that results in a synergic effect. However, approximate models can be identified that are sufficiently accurate for controller design provided that the experimental conditions remain similar.

Goodness of predictive accuracy of the resulting combined PKPD models was affected not only by the identified PD model parameters but also by the PK model, i.e, the predicted plasma propofol concentration $C_p$. Both Paedfusor and Kataria PK models are population-based models, and their predictive performance is significantly limited by the large PK and PD inter-individual variability in the pediatric population. When the real PK is significantly different from the PK model, the model-predicted $C_p$ becomes an unreliable estimate of the actual plasma propofol concentration. Since blood samples were not collected in this study, it was not possible to assess the adequacy of the PK model. However, further examination of the PD modeling results showed that the correlation between SE and $C_p$ was weak in some subjects. For these subjects, the prediction accuracy of the final combined PKPD model was usually unsatisfactory, implying that the accuracy of the PK model may be a limiting factor of the PD modeling.

The clinical study described in this chapter was not primarily designed for the purpose of PD model identification, and some aspects of the experimental protocol were not optimally designed for this purpose. For example, the PD model identification in in Study 1 and Study used a constant
infusion profile of propofol. In theory, high-fidelity system identification necessitates the use of persistently exciting inputs [51]. The spectral contents of the constant infusion profile are mostly concentrated in the low-frequency range. This may have imposed some limitations on the identification accuracy of $k_{c0}$. For future PD models, it is recommended to design and conduct clinical studies for the sole purpose of PD models identification.
3. A Monitor-Decoupled Pharmacodynamic Model of Propofol

The PK and PD models are used extensively to predict and control the clinical endpoints of interest, such as depth of hypnosis, based on estimates of the propofol concentration in the plasma or effect compartment [52]. However, their predictive capacity and control efficacy will be deleteriously affected by the bias caused by the dynamic and nonlinear behavior of the depth of anesthesia monitor, which is unrelated to the patient response. Currently, the dynamic and nonlinear behavior of the depth of anesthesia monitors are not explicitly considered in developing PD models. The resulting PD model implicitly includes the dynamics of the depth of anesthesia monitors in addition to the PD model that directly describes the patient response. The dynamics of most of the monitors are not negligible. For instance, the BIS monitor often introduces a significant and variable time delay in its response due to
the complexity of its signal processing and decision algorithm [53]. Some researchers in the field have considered a fixed delay in the PD identification process [54] to account for this complex challenge. However, a more systematic and rigorous approach is required to fully address the adverse effects related to the monitor dynamics.

In an attempt to improve prediction reliability, this chapter presents a new monitor-decoupled approach to PD modeling. In this framework, the dynamics of the monitor are characterized and explicitly accounted for in the PD modeling process. To demonstrate our idea, we used the depth of anesthesia index, State Entropy (SE) that is measured by the Entropy monitor. First, a linear time-invariant dynamic model of the Entropy monitor was derived as an ARX model using a system identification procedure. Second, this monitor model was excluded from the patient PD model by adding it as a separate component from the traditional PD model.

This chapter is organized as follows. Section 3.1 describes monitor dynamics associated with the M-Entropy Monitor. Section 3.2 presents a detailed discussion of the monitor-decoupled approaches to PD modeling. Transport delay is introduced in the model and estimated in Section 3.3. Sections 3.4, 3.5 and 3.6 present the results of cross validation, parameter estimation and covariate analysis respectively. Results are discussed in Section 3.7.

3.1 Monitor Dynamics

The key feature of the proposed monitor-decoupled PD model, compared with its traditional counterpart, is the presence of the monitor model H(s), see Figure 3.1. To build the monitor-decoupled PD model, H(s) may be characterized in advance. Once H(s) is obtained, the remaining procedure is similar to the traditional PD modeling. To build a dynamic model describing the monitor dynamics, five distinct EEG segments from volunteers and patients, undergoing anesthesia procedures were acquired. These segments correspond to various levels of cortical activity: active/awake, drowsy/sedated [55]. Each of these EEG measurements was processed off-line by the Entropy monitor.
to obtain the value of SE associated with each cortical activity level. The EEG measurements were then combined in a random order and processed by the Entropy monitor. The output of the Entropy monitor in response to the combined EEG segments can be viewed as the response of the Entropy monitor to multiple step inputs (where the value of each step input is the SE value obtained for the corresponding EEG segment). The Entropy monitor model, \(H(s)\), was identified to describe the dynamic relationship between the multiple step SE inputs and the corresponding output sequences.

\[
H(s) = e^{-T_d s} \frac{K_d}{s + K_d}.
\]

Figure 3.1: (a) The Traditional PD model. (b) The Monitor-decoupled model.

A linear time-invariant model structure was assumed for \(H(s)\). Using the MATLAB System Identification Toolbox (MATLAB System Identification Toolbox User’s Guide, MathWorks, 2008) the dynamic input-output relationship was approximated using an ARX model. A maximum order of 10 for the denominator and numerator was considered in the system identification procedure. In addition, a transport delay of up to 5s was permitted. Iterative system identification trials resulted in the following delay-plus-2\(^{nd}\)-order transfer function as the representation of \(H(s)\):

\[
H(s) = e^{-t} \frac{0.61s + 0.39}{s^2 + 3.77s + 0.40}.
\]  

(3.1)

\(H(s)\) was then transformed into a discrete-time transfer function \(H(z)\) with a 5s sampling interval that is compatible for use with the SE measurements collected from the data accumulated from
the subjects in this study. The discrete-time model of the Entropy monitor $H(z)$ thus obtained was used for the monitor-decoupled PD modeling.

### 3.2 Monitor-Decoupled Modeling

The PD model was identified for 1) each individual and 2) both the Paedfusor and the Kataria PK models, as presented in the previous chapter, with data from Section 2.3.1 [42]. The PD identification steps were as follow:

1. The range of $k_{e0}$ search was limited within $0 < k_{e0} < 10$.
2. For each candidate value of $k_{e0}$ in the search space, the effect site propofol concentration was calculated using (1). Based on an assumed set of values of $EC_{50}$ and $\gamma$ the clinical effect $\hat{E}_D(t)$ was predicted using (2.6). In contrast to the traditional PD modeling explained in 2.1.2, where $\hat{E}_T(t)$ was directly used to identify PD model parameters, here, $\hat{E}_T(t)$ was filtered through $H(z)$ to yield the predicted SE, $\hat{E}_D(t)$. In the context of the monitor-decoupled model, therefore, $\hat{E}_D(t)$ is the true PD response of the patient whereas $\hat{E}_T(t)$ is the measurement provided by the Entropy monitor.
3. The values of $EC_{50}$ and $\gamma$ that minimize the mean-squared error between measured $E(t)$ versus predicted $\hat{E}_T(t)$ for SE were identified for each $k_{e0}$ in the search space. The optimal set of PD model parameters was determined by minimizing these mean-squared SE prediction errors over $k_{e0}$. In other words, the optimal set of PD model parameters was the solution to the following optimization problem:

$$
\Theta^* = \left\{ k_{e0}^*, EC_{50}, \gamma^* \right\} = \arg \min_{\Theta = \left\{ k_{e0}, EC_{50}, \gamma \right\}} \left\| E(t) - \hat{E}_D(t) \right\|.
$$

### 3.3 Transport Delay Estimation

Figure 3.2 show that some SE responses exhibit a noticeable delay in the beginning of the induction profile. In order to investigate if the inclusion of an additional delay in the PD model as a
separate model parameter further improve the model fidelity and reduce inter-individual variability, we also considered the following delay-plus-1st-order model as the relationship between \( C_e \) and \( C_p \), where \( k_d \) is the effect dynamics:

\[
 C_e(s) = e^{-T_d s} \frac{k_d}{s + k_d} C_p(s).
\]

In this model, the transport delay \( T_d \) is intended to capture the possible existence of pure time delay in the plasma-effect site equilibration process. The monitor-decoupled PD model identification was repetitively conducted using the values of \( T_d \) between 0s and 25s with 5s increments.

![Figure 3.2: Individual progression of SE response for each subject in the study.](image)

### 3.4 Cross-Validation of the Sate Entropy Dynamic

As explained in section 3.1, SE values associated with each cortical activity level were obtained. Two different sets of data from this group were used in the identification and validation of
H(s). The data used in the system identification contained more high-frequency content than the cross validation data in order to intensively excite the Entropy monitor to build a high-fidelity model, see Figure 3.3. On the other hand, the cross-validation data consisted largely of slow changes that are commonly observed during stable anesthesia. This may be more appropriate to assess the predictive performance of the model in real clinical scenarios. Residual analysis compared the performance of the PD models identified in this study. Residuals were computed as the difference between measured versus predicted SE, and the error was reported as the mean squared error (MSE):

\[
MSE = \frac{\sum (E(t) - \hat{E}(t))^2}{n},
\]

(3.4)

where \(n\) is the number of subjects.

To accurately assess if the calculated MSE values are statistically different between the proposed and traditional methods, the t-test was applied. With the t-test, we judge the difference between the MSE values relative to the spread or variability of the measured values.

### 3.5 PD Parameter Identification

The individual progression of the SE response to propofol infusion was highly variable even though the variability in the baseline was relatively negligible, see Figure 3.2. Using the MATLAB System Identification Toolbox (MATLAB System Identification Toolbox User’s Guide, MathWork, 2008), the true SE response based on the used data set and the predicted SE response based on the response filtered by \(H(s)\) are presented in Figure 3.4 and Figure 3.5. The linear time-invariant approximation of the Entropy monitor (3.1) provided a 61.1% fit to the data used in the system identification, and 85.5% fit to cross-validation data that was not shown to the model in the system identification phase.
Figure 3.3: Multi-step SE inputs and the corresponding output sequences from the Entropy monitor used for H(s) identification.
Figure 3.4: True versus predicted responses of Entropy monitor to the data used in system identification.

Figure 3.5: True versus predicted responses of Entropy monitor to the data used in cross validation.
The identified model of the Entropy monitor behaves very well in response to slowly changing EEG activity. However, its accuracy is expected to deteriorate if the EEG activity is rapidly changing. The identified PD model parameters based on the monitor-decoupled PD modeling are summarized in Table 3.1 and Table 3.2 where for comparison, the results from the two-stage approach as presented in previous chapter are also included.

<table>
<thead>
<tr>
<th>PK Model</th>
<th>$k_{e0}$ [min$^{-1}$]</th>
<th>EC$_{50}$ [mcg/ml]</th>
<th>$\gamma$</th>
<th>$T_{peak}$ [s]</th>
<th>MSE [e$^{-3}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor-decoupled</td>
<td>5.4±3.0</td>
<td>4.6±0.8</td>
<td>5.5±1.7</td>
<td>52.3±20.1</td>
<td>5.5±2.8</td>
</tr>
<tr>
<td>Two-stage</td>
<td>3.0±1.9</td>
<td>4.7±0.8</td>
<td>5.2±1.4</td>
<td>66.0±23.5</td>
<td>5.4±2.8</td>
</tr>
</tbody>
</table>

**Table 3.1: Identified PD model parameters based on a monitor-decoupled PD modeling for Paedfusor [42].**

<table>
<thead>
<tr>
<th>PK Model</th>
<th>$k_{e0}$ [min$^{-1}$]</th>
<th>EC$_{50}$ [mcg/ml]</th>
<th>$\gamma$</th>
<th>$T_{peak}$ [s]</th>
<th>MSE [e$^{-3}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor-decoupled</td>
<td>2.3±1.4</td>
<td>3.5±0.6</td>
<td>4.6±1.4</td>
<td>67.7±19.7</td>
<td>6.1±3.1</td>
</tr>
<tr>
<td>Two-stage</td>
<td>1.4±0.8</td>
<td>3.5±0.6</td>
<td>4.3±1.3</td>
<td>85.9±18.7</td>
<td>6.1±3.0</td>
</tr>
</tbody>
</table>

**Table 3.2: Identified PD model parameters based on a monitor-decoupled PD modeling for Kataria [42].**

For both Paedfusor and Kataria PK models, the values of $k_{e0}$ identified for each individual were consistently larger than their traditional counterparts (t-test resulted in $p<0.001$ for Paedfusor and $p<0.01$ for Kataria PK models). This is an expected outcome, considering that:

1. The monitor dynamics have low-pass filter characteristics.
2. The dynamics of the Entropy monitor are implicitly lumped into $k_{e0}$ in the traditional PD model but are explicitly considered as the monitor model in the monitor-decoupled PD model.
In contrast, the values of EC$_{50}$ and $\gamma$ were comparable between the monitor-decoupled and traditional PD models. In terms of predictive accuracy, the Two-stage versus monitor-decoupled PD models exhibited no significant differences as presented by MSE values in Table 3.1 and Table 3.2. For both Paedfusor and Kataria PK models, the individual values of MSE associated with traditional and monitor-decoupled PD models were highly comparable to each other.

Table 3.3 summarizes the PD model parameters obtained from the monitor-decoupled PD modeling with an additional PD transport delay. The identified value of the delay was 1.5(4.1) and 7.5(6.7) seconds for Paedfusor and Kataria models, respectively. Overall, the Kataria PK model incurred significantly larger delay compared with the Paedfusor PK model ($p<0.001$). The major consequence of including the PD transport delay in the PD model was the increase in the equilibration rate constant $k_d$. In contrast, EC$_{50}$ and $\gamma$ were remarkably consistent and independent of the PD transport delay. Incorporating the PD transport delay improved the predictive accuracy of the resulting model (as indicated by the reduction of MSE compared to Table 3.3).

<table>
<thead>
<tr>
<th>PK Model</th>
<th>$k_d$ [min$^{-1}$]</th>
<th>EC$_{50}$ [mcg/ml]</th>
<th>$\gamma$ [s]</th>
<th>T$_{peak}$ [s]</th>
<th>MSE [$e^{-3}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paedfusor</td>
<td>5.8±2.9</td>
<td>4.6±0.8</td>
<td>5.8±1.8</td>
<td>41.1±16.4</td>
<td>5.4±2.8</td>
</tr>
<tr>
<td>Kataria</td>
<td>3.0±1.8</td>
<td>3.4±0.6</td>
<td>4.6±1.4</td>
<td>56.6±18.4</td>
<td>5.7±3.0</td>
</tr>
</tbody>
</table>

Table 3.3: Identified PD model parameters based on a Monitor-Decoupled PD model with extra PD transport delay [42].

3.1 Covariates Analysis

The dependence of $k_{e0}$ on age and weight was evaluated using the coefficient of determination ($r^2$ value). The values of $k_{e0}$ derived for individual patients were plotted against age and weight, and the plots visually inspected for correlations. The correlation coefficient was also numerically

The correlation coefficient calculated for $k_{e0}$ with age and weight indicated its weak dependence to these prospective covariates see Table 3.4 and Table 3.5 and also Figure 3.6 Also, the calculated correlation coefficient for $EC_{50}$ and $\gamma$ did not indicate a strong correlation to age and weight. It was concluded that $k_{e0}$, $EC_{50}$ and $\gamma$ are dependent upon neither age nor weight in the ranges included in the study (t-test resulted in $p<0.001$ for Paedfusor and Kataria PK models). This weak correlation can be attributed to the high inter-individual PD variability in the pediatric population, as well as the narrow range of age and weight of the study population.

<table>
<thead>
<tr>
<th></th>
<th>$k_{e0}$</th>
<th>$EC_{50}$</th>
<th>$\gamma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.19</td>
<td>0.35</td>
<td>0.21</td>
</tr>
<tr>
<td>Weight</td>
<td>0.08</td>
<td>0.03</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Table 3.4: Covariate analysis for Paedfusor Model, Correlation coefficient of PD parameters to age and Weight

<table>
<thead>
<tr>
<th></th>
<th>$k_{e0}$</th>
<th>$EC_{50}$</th>
<th>$\gamma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.08</td>
<td>-0.18</td>
<td>0.40</td>
</tr>
<tr>
<td>Weight</td>
<td>0.18</td>
<td>-0.52</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Table 3.5: Covariate analysis for Kataria. Model, Correlation coefficient of PD parameters to age and Weight.
Figure 3.6: Covariate analysis for $k_{e0}$ a) Paedfusor model $k_{e0}$, b) Kataria model $k_{e0}$. 
Figure 3.7: Covariate analysis for EC_{50} a) Paedfusor model EC_{50}, b) Kataria model EC_{50}. 
Figure 3.8: Covariate analysis for $\gamma$, a) Paedfsor model $\gamma$, b) Kataria model $\gamma$. 
3.2 Discussion

In this chapter, we have presented a novel method to decouple the PD response from the bias caused by the dynamic and nonlinear characteristics of the monitor equipment. The presented model decouples the dynamic delay introduced by the monitor and significantly increases the $k_{e0}$, which predicts a more rapid clinical effect but does not change the other model parameters. The results suggest that it may be beneficial to explicitly consider the effects of the monitor dynamics when identifying a PD model. We chose to identify PD models for each individual, and the PD modeling was conducted for two popular pediatric PK models of propofol: Paedfusor and Kataria models. While only the Entropy monitor was explored in our study, the modeling framework is generic and can be readily applied to other monitors such as BIS, assuming they can be reasonably well modeled.

Comparing the monitor-decoupled versus two-stage (refer to as traditional from now) PD models reveals that decoupling the effect of the monitor equipment from the PD response of the patient significantly increases $k_{e0}$, see Table 3.1 and Table 3.2. It was expected that the use of the traditional PD model would predict a delayed patient response (i.e., pure patient response retarded by the monitor’s processing delay) since $k_{e0}$ of the traditional PD model implicitly includes the processing delay associated with the monitor equipment. On the other hand, the pure patient response can be easily predicted using the monitor-decoupled PD model because it explicitly accounts for the monitor dynamics (i.e., $H(s)$ in Figure 3.1b) in the model and can be used to compare results from different monitors.

This observation was consistent for both Paedfusor and Kataria PK models, see Table 3.1 and Table 3.2. In contrast, the values of $EC_{50}$ and $\gamma$ were highly comparable between traditional and monitor-decoupled PD models, suggesting that the Entropy monitor dynamics mainly affect $k_{e0}$ but do not significantly alter the dose-response relationship in the steady-state. In essence, the difference in the PD model parameters between the two approaches suggests that it may be beneficial to explicitly
consider the effect of the Entropy monitor or even other measures of EEG effect, such as BIS, when identifying a PD model.

The monitor-decoupled PD modeling was also used to examine the existence of a PD transport delay, using the delay-incorporated PD model (3.3). By explicitly considering the PD transport delay, the associated equilibration rate constant $k_d$ was identified to be larger than $k_{e0}$ corresponding to the absence of the transport delay. It also improved the predictive capacity of the model, although it did not reach statistical significance. The values of $k_d$ being larger than $k_{e0}$ can be interpreted as follows: if a PD model without the PD transport delay, is used, the transport delay in the PD response is implicitly lumped into $k_{e0}$. Since $k_{e0}$ has to contain the same phase shift as the combination of both $k_d$ and the PD transport delay, it will have to assume smaller values compared to $k_d$. Physiologically, the PD transport delay can be regarded as the phase delay involved in the distribution of propofol during the initial uptake phase.

The potential inaccuracy in $k_{e0}$ may have affected the accuracy of $EC_{50}$ and $\gamma$. However, the results shown in Tables 3-1, 3-2 and 3-3 indicate that the values of $EC_{50}$ and $\gamma$ are highly consistent over different PD models. This suggests that $EC_{50}$ and $\gamma$ were identified with high fidelity. The steepness of the dose-response curve, with very few points on the steep part of the curve, may have limited the ability to capture the dynamics of the induction phase.
4. Robust Model Predictive Control in Anesthesia

To reach the goal of closed-loop control of hypnosis we have chosen the model predictive controller (MPC). In simple terms, the MPC strategy can be stated in two steps. Firstly, it uses a process model to predict the evolution of the process output as a function of future control actions and secondly, it minimizes (over these control actions) a specified cost index; this cost includes the errors between the desired and predicted process outputs, and possibly also the required control effort [56]. The MPC control strategy has the inherent ability to handle multivariable control problems and to allow constraints to be imposed on both the controlled and manipulated variables.

MPC has been successfully implemented in many applications in the chemical industry [57] and use of MPC has been proposed for the control of blood glucose [58] and anesthesia drugs [59], [60], [25]. Closed-loop control of hypnosis using MPC in adults has been evaluated in simulation [59], [60] as well as in a clinical study [25]. A control system using an individualized MPC controller augmented by a ‘risk control’ supervisory system was evaluated in 79 clinical cases [25]. The
proposed controller was evaluated in simulation prior to the study, where plant-model mismatches were introduced. However, formulation of robust stability and performance guarantees for this adaptive approach is technically challenging. An extended prediction self-adaptive control algorithm (EPSAC) was compared to an adaptive controller in simulation [59]. The dynamics of the models do not take the inter-patient variability observed in PKPD studies into account, and the uncertainty description used in this study possibly underestimates the variability observed in practice. In [61] Ionescu et al. proposed a method to verify robustness towards patient uncertainty after the controller was designed. This is a limitation of this system, since for a certifiable design; robust analysis will have to part of the design stage. Also the considered inter-patient variability in the mentioned study is limited.

The goal of this chapter is: 1) to design a robust MPC controller for adults (MPC\textsubscript{adult}) that provides adequate propofol infusion for the complete study population, 2) to compare the MPC\textsubscript{adult} with previously published robust designs and check the feasibility of achieving similar performance with an MPC design that can easily be extended to constrained and multivariable control, 3) to define a nominal model and uncertainty description in children, and 4) to design a robust MPC controller for children (MPC\textsubscript{child}) that can meet clinical criteria [62].

### 4.1 The Model Predictive Control principle

In an MPC design:

1. At each current moment \( t \), the predicted output \( y(t+k) \) is predicted over a time horizon \( k=1\ldots N_2 \). The prediction is based on the model of the process and the forecast depends on the past inputs and outputs, but also on the future control scenario \( u(t+k|t) \), \( k=1\ldots N_2-1 \).
2. A reference trajectory \( r(t+k|t), k=1\ldots P \). starting at \( r(t|t)=y(t) \) and evolving towards the set-point \( w(t) \) is defined over the prediction horizon. \( r(t) \) describes how we want to guide the process output from its current value \( y(t) \) to its set-point \( w(t) \).

3. The control vector \( u(t+k|t) \) is calculated in order to minimize a specified cost function, depending on the predicted control errors \( \{ r(t+k|t) - y(t+k|t), k=1\ldots N_2 \} \). There could also be some structuring of the future control law and might also be constraints on the process variables.

4. Only the first element of the optimal control vector \( u(t|t) \) is applied to the real process. At the next sampling instant a new output measurement is obtained and the whole procedure is repeated.

Figure 4.1 presents the five MPC principles in a simple diagram. The various algorithms, members of the large MPC-family, differ mainly in:

1. the type of model used to represent the process and its disturbance;
2. the cost function(s) to be minimized, with or without constraints.

![Figure 4.1: The MPC principle,][56]
The present study is confined to the control of the depth of hypnosis by adjusting the infusion rate of propofol during anesthesia. In this chapter, an MPC controller that includes robustness in the design step is presented for adults and children assuming that no constraints are active. The results of a consecutive study with constraints on drug concentrations and physiological parameters in closed-loop control of propofol are presented in Chapter 5.

4.2 Experimental Protocol

In this study the model set described by Dumont et al [3] and the model set identified by van Heusden et al. [63] are used for adults and children (Ethics Certificate H11-02952) respectively. The adult model set includes 44 models, identified from data from 18-60 yr adults with an ASA status of I or II. The mean (SD) age and weights were 36(12) yr and 80(14) kg. The model set for children is identified from data from 47 children age 6-16 year, ASA I-II, requiring general anesthesia. The mean (SD) age and weights were 12(3) yr and 44(16) kg. The adult models use the 3-compartment PK model of Schüttler [37] and pediatric models use the Paedfusor PK model by [38] to predict the propofol plasma concentration ($C_p$) as a function of the infusion rate ($u$)

4.3 Nominal Model

MPC requires a process model to predict the future output values. The performance of MPC is strongly dependent on the quality of this process model and hence the definition of the model and quantification of the uncertainty around it is critical. Following the approach presented in [3], the nominal model $\text{PKPD}_n (T_{do}, K_n, z_{o1}, z_{o2}, p_{o1}, p_{o2}, p_{o3}, p_{o4}, \text{zero-pole-gain parameters})$ is constructed from the individual frequency responses of all patients in the study. A summary of the nominal parameters is presented in Table 4.1 To minimize the uncertainty, the parameters of $\text{PKPD}_n$ are tuned by minimizing the difference between the patients and the nominal frequency response using:
Robust Model Predictive Control in Anesthesia

\[
\begin{align*}
\min_{\theta} & \sum_{j=1}^{n} \left| PKD_j(j \omega) - PKD_j(j \omega) \right|, \\
\text{s.t.} & \quad lb \leq \theta \leq ub
\end{align*}
\]  

(4.1)

where \( n \) is the number of patients in the group and \( \theta = (T_{do}, K_{do}, z_{1o}, z_{2o}, p_{1o}, p_{2o}, p_{3o}, p_{4o}) \) represents the optimum parameters of the nominal model and \( lb = \min (T_{do}, K, z_{1}, z_{2}, p_{1}, p_{2}, p_{3}, p_{4}) \) and \( ub = \max (T_{do}, K, z_{1}, z_{2}, p_{1}, p_{2}, p_{3}, p_{4}) \) are the lower and upper bounds respectively.

### 4.4 Controller Design

The nominal model obtained after discretization can be represented as a state-space model, the popular MPC formulation in the research literature [64]. Maciejowski [56] showed that for every transfer function formulation of an MPC there is an equivalent state-space formulation. He further claimed that “there seems to be no reason for using transfer functions” as formulation of the predictive control particularly in MIMO MPC:

In the current study, the disturbance is assumed to act on the output and \( \eta(k) \) was defined as the disturbed output and \( y(k) \) represents the actual measured output [56]. The setup for closed-loop control is shown as a schematic diagram in Figure 4.2. To obtain offset-free tracking, the model was augmented by defining a new state vector, \( \varepsilon(k) \) and an augmented model:

\[
\varepsilon[k] = \begin{bmatrix} \Delta x(k) \\ \eta(k) \end{bmatrix},
\]

(4.2)

\[
\begin{bmatrix} \Delta x(k + 1) \\ \eta(k + 1) \end{bmatrix} = \begin{bmatrix} A_s & 0 \\ CA & 1 \end{bmatrix} \begin{bmatrix} \Delta x(k) \\ \eta(k) \end{bmatrix} + \begin{bmatrix} B_s \\ CB \end{bmatrix} \Delta u(k) + \begin{bmatrix} 0 \\ 1 \end{bmatrix} w(k)
\]

(4.3)

where \((A_s, B_s, C_s)\) is the state-space representation of the augmented model, \( G_s \), \( w(k) \) and \( v(k) \) are the output disturbance and white measurement noises.
Figure 4.2: Schematic of the closed-loop control system. The DOH monitor provides a measure of the clinical effect and DOH Reference is the setpoint set by the anesthesiologist. The infusion pump delivers propofol to the patient, where the optimized infusion rate is calculated by the MPC controller. The stimulation from the procedure affects the measured DOH index.

The augmented state vector cannot be measured and is therefore estimated, using the one-step ahead steady-state Kalman filter. From the predicted state, the predicted output \( y(k) \) is calculated. The output in a compact matrix form is

\[
Y = F\hat{e}(k) + \Phi \Delta U,
\]

where \( \hat{e} \) is the estimated state, \( \Delta U \), \( Y \) and \( F \) and matrix \( \Phi \) are defined as follow:

\[
\Delta U = \begin{bmatrix}
\Delta u(k) & \Delta u(k+1) & \ldots & \Delta u(k+n_c-1)
\end{bmatrix}^T.
\]

\[
Y = \begin{bmatrix}
y(k+1) & y(k+2) & \ldots & y(k+n_p|k_i)
\end{bmatrix}^T.
\]

\[
F = \begin{bmatrix}
C_x A_x & C_x A_x^2 & \ldots & C_x A_x^{n_c}
\end{bmatrix} \quad \Phi = \begin{bmatrix}
C_x B_s & \ldots & 0
C_x A_x B_s & \ldots & 0
\vdots & \ddots & \ldots & \vdots
C_x A_x^{n_c-1} B_s & \ldots & C_x A_x^{n_p-n_c} B_s
\end{bmatrix}
\]

where \( n_c \), the control horizon, is the number of samples used to capture the future control trajectory and \( n_p \), the prediction horizon is the length of the optimization window.
The control objective is to minimize a performance index involving the difference between the given set-point signal $r(k)$ and the $y(k)$ within a prediction horizon. In this study, the only constraint used is on the amplitude of control variable $u(k)$, i.e., the propofol infusion rate:

$$\min_{\Delta u(k)} \sum_{i=0}^{N} |y(k) - r(k)|_Q^2 + \sum_{i=0}^{N-1} |\Delta u(k)|_R^2,$$

$$\text{s.t. } u_{\text{min}} \leq u(k) \leq u_{\text{max}}$$

where $Q$ and $R$ are weights of output error and input rate respectively.

### 4.5 Robust Stability and Nominal Performance

Probably the most challenging part in closing the loop in anesthesia is dealing with patient variability. It is necessary to quantify and express this variability as a system uncertainty in order to prove stability. In this work, robustness is defined with respect to PKPD model uncertainty and a fixed linear controller. Factors resulting in uncertainty in PKPD include: age, weight, height, and medical history.

#### 4.5.1 Uncertainty Model

Two main approaches can be considered when quantifying system uncertainty:

- **Parametric uncertainty**: uncertainty is defined by considering bounded real deviations in system parameters. Parametric uncertainty supposes that each model parameter can take any value from the defined uncertainty range. In the case of PKPD, this may lead to a combination of parameters that is not (physiologically) possible.

- **Unstructured uncertainty**: only the overall uncertainty in terms of the gain and phase of the system is defined. The unstructured framework is considered when the model structure itself is poorly defined, or when the uncertainty cannot be expressed as parametric uncertainty.

In considering PKPD uncertainty, the unstructured uncertainty approach was considered in this thesis. This uncertainty in the frequency domain is represented by multiplicative uncertainty, where magnitude of it, $l_1(\omega)$ is calculated as:
Robust Model Predictive Control in Anesthesia

\[ l_c(\omega) = \max_{G_p \in \Pi} \left| \frac{G_p(j\omega) - G_n(j\omega)}{G_n(j\omega)} \right| \quad \forall \omega, \quad (4.6) \]

where \( G_n \) is the nominal plant model with no uncertainty, \( G_p \) is a particular patient model and \( \Pi \) is the set of all patient models.

### 4.5.2 Sensitivity Functions

Robustness to model uncertainties is reflected in the sensitivity function and the complementary sensitivity function based on the loop transfer function of the feedback system, \( L \). The sensitivity functions are defined as:

- **Sensitivity function:** \( S = (1 + L)^{-1} \)
- **Complementary Sensitivity function:** \( T = L(1 + L)^{-1} \) \quad (4.7)

![Block diagram of the closed-loop system](image)

**Figure 4.3:** Block diagram of the closed-loop system, where \( r(t) \) is the reference depth of hypnosis set by the anesthesiologist, \( u(t) \) is the infusion rate calculated by the controller, \( d(t) \) represents the stimulation from the procedure and \( y(t) \) is the depth of hypnosis output.

<table>
<thead>
<tr>
<th></th>
<th>( T_d )</th>
<th>( K )</th>
<th>( Z_{1o} )</th>
<th>( Z_{2o} )</th>
<th>( P_{1o} )</th>
<th>( P_{2o} )</th>
<th>( P_{3o} )</th>
<th>( P_{4o} )</th>
</tr>
</thead>
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<td>1.8</td>
<td>1.5</td>
<td>3.7</td>
<td>2.5</td>
<td>6.7</td>
<td>2.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Child</td>
<td>48</td>
<td>1.3</td>
<td>0.9</td>
<td>5.2</td>
<td>2.0</td>
<td>5.0</td>
<td>4.9</td>
<td>3.9</td>
</tr>
</tbody>
</table>

**Table 4.1:** Optimum Identified Nominal Parameters.
Robust Stability (RS) and Nominal Performance (NP) are guaranteed if:

\[
\begin{align*}
\text{RS} & \iff \|\Gamma(\omega)\| < \frac{1}{w_I} \quad \forall \omega \\
\text{NP} & \iff \|S(\omega)\| < \frac{1}{w_P} \quad \forall \omega
\end{align*}
\]

(4.8)

where \( w_I \) is the multiplicative uncertainty weight and \( w_P \) is the performance weight.

The requirement of robust stability with multiplicative uncertainty gives an upper bound on \( T \).

To represent unmodelled dynamics, \( w_I \) is determined by [65]:

\[
w_I(s) = \frac{\frac{\omega_m}{\tau} + r_0}{(\frac{\tau}{r_0})s + 1},
\]

(4.9)

s.t. \( w_I(j\omega) \geq l_1(\omega) \quad \forall \omega \)

where \( r_0 \) is the relative uncertainty at steady state, \( 1/\tau \) is approximately the frequency at which the relative uncertainty reaches 100%, and \( r_0 \) is the magnitude of the weight at high frequency, [65]. The uncertainty, \( l_1(\omega) \), and \( w_I \) are shown in Figure 4.4 derived using the nominal model identified earlier.

To provide a clinically acceptable response, the anesthesia procedure should start with a fast induction with minimal overshoot. In engineering principles the specifications of the system for this work were defined as an overshoot of less than 15% and an initial rise time of less than 5 minutes. To meet the overshoot specification, the maximum value of the sensitivity function, \( M_s \), is limited to \( < 2 \) [66]. The weight \( w_P \) is defined as an upper bound on the sensitivity \( S \), based on \( \omega_m \), the minimum bandwidth frequency, \( E_S \) the maximum steady error and \( M_s \) state error and \( M_s \) [65]:

\[
w_P(s) = \frac{s/M_s + \omega_m}{s + \omega_m E_S},
\]

(4.10)

where \( M_s = \max_\omega |S(j\omega)| \)
Figure 4.4: Relative errors for a) 44 adults and b) 47 children (solid blue lines) $l_1$ (solid green) and $w_1$ (dashed red line) are plotted.
The robust control theory considered here, assumes that no constraints are active. This hypothesis will be met when the MPC controller operates in its unconstrained mode, hence linear control, which is the case during most of the procedure [56].

4.6 Robust Tuning of Model Predictive Control

Different tuning methods and formulations are available for designing a robust MPC [67], [68]. It should be noted that the goal of this work is not to find the global best tuning approach for MPC, but rather an appropriate MPC tuning for automatic control of hypnosis. The tuning parameters of the MPC controller \( n_p \), \( n_c \), and \( R \), as well as the parameters for the Kalman filter are tuned in a systematic way to meet the specifications. In a first step, the Kalman filter parameters, \( R_w \) and \( R_v \), are tuned. This is achieved with a preliminary tuned MPC controller. The covariance of NeuroSENSE measurement noise is set to \( R_v = 9.0 \) as described by Soltesz et al [28]. Based on this particular \( R_v \) value, the covariance \( R_w \) is identified to optimize the output predictive capability of the Kalman filter by minimizing the difference between the observed output from NeuroSENSE, \( Y_{obs} \) and the predicted output from Kalman filter \( Y_{est} \) such that robust stability and nominal performance holds:

\[
\min_{R_w} \sum |Y_{obs} - Y_{est}|
\]  

(4.11)

In a second step, the MPC parameters are tuned. Increasing \( n_c \), increases the degree of freedom in calculating the control move. A longer control horizon, results in a faster system response at the cost of the system being less robust [69]. Penalizing \( \Delta u \) with \( R \), results in a more robust controller at the price of the controller being sluggish [70]. Altering \( n_p \), concerns a trade-off between the rise-time and the overshoot upon induction of anesthesia. Increasing \( n_p \) has a stabilizing effect but also increase the computational effort. According to Algorithm 1, the parameters were tuned to optimize performance while meeting the robustness criteria.
- Initialize the preliminary MPC parameters.
- Fix $R_v$ value, and select $R_w$ by minimizing the difference between $Y_{obs}$ and $Y_{est}$ using (4.11).
- For MPC parameter: { $n_c$, $R$, $N_p$ }:
  - While conditions for (4.8) are satisfied:
    - Evaluate time-domain performance by calculating rise-time and overshoot values.
    - Evaluate $M$, $M_s$.
    - Select the parameter which results in lowest $M$, value when rise-time and overshoot specifications are met.
- end
- end

**Algorithms 1: MPC Tuning Algorithm**

### 4.7 Tuning Parameters

For the preliminary tuned controller, the prediction horizon was fixed to $n_p=60$ samples, corresponding to the 5 minutes induction time with sampling time of $t_s=5$ seconds. The remaining MPC parameters were chosen as $n_c = 1$, and $R=1$. Minimization for Kalman filter tuning was performed with $R_w$ values in the range 0.01-10 where predictability of the filter improved with increasing value of $R_w$. With $R_c$ values fixed to 9.0, increasing $R_w$, increased the observer gain meaning that for a noisy output, the gain will amplify the noise in the output. $R_w$ was set to 1 to provide accurate predictions while keeping the observer gain small.

MPC parameter tuning started with $n_c$. Increasing the control horizon to $n_c = 2$ resulted in a faster rise-time. The system remained stable and the added computational cost was negligible. For $n_c$ values greater than 2, the nominal system was unstable. The effect of changing $R$ was examined for values between 0.1-1. The controller attained robust stability and nominal performance with all the values in the range. For $R$ value 0.3, the system achieves a fast induction with no initial overshoot. With $n_c = 2$, $R_w = 1$, $R_c = 9$, $R = 0.3$, $n_p$ values between 40 to 100 were considered. The controller achieved robust stability and nominal performance for all $n_p$ values in the specified range. The
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prediction horizon, \( n_p \) was fixed at 70 as the system achieves the smallest \( M_s \) value with that tuning parameter. This manually tuned controller satisfies the robust stability requirement and the nominal performance requirement as shown in Figure 4.5 a.

Following Algorithm 1 and the same tuning guideline described for adults, the MPC controller for children is tuned with parameters set to \( n_c = 2, R_w = 0.01, R_v = 9, R = 0.3, n_p = 50 \). The robust stability and nominal performance conditions and the sensitivity plots are presented in Figure 4.5 b.

Figure 4.5 Closed-loop sensitivity and complementary sensitivity analysis for the nominal system, a) adults, b) children.
4.8 Results

For each controller, a 60 minute surgical procedure was simulated for the complete set of models assuming an infusion of 10 mg/ml propofol. Simulations are performed using nonlinear patient models. The target depth of hypnosis was set to a $WAV_{CNS} 50$ for the duration of the procedure. For all patients, a hypothetical surgical stimulus is fixed to start 20min after the beginning of the simulation. This stimulus profile was adapted from [71] and is shown in Figure 4.6. The infusion rate in this study is constrained between $u_{\text{min}}=0$ and $u_{\text{max}}=1200\text{ml/hr}$ which is the maximum infusion rate of the propofol pump.

![Figure 4.6: Surgical stimulus profile [3].](image-url)
For assessment of the adult MPC controller, results are compared to the results from the controller by Hahn et al [71]. The nominal model in both designs is constructed from the PK model by Schüttler and characteristic data and PD parameters from [3]. For the controller by Hahn et al, the controller is also fixed for all patients and the patient models are divided into four age groups (Gr 1: 18-30 yr, Gr 2: 31-40 yr, Gr 3: 41-50 yr, and Gr 4: 51-60 yr) to also investigate the effect of age as a covariate. Results from the MPC controller for children are compared with the results from the clinical evaluation of a PID controller by van Heusden et al [29]. The controller in both designs use the Paedfusor PK model and PD parameters from [63]. In the van Heusden et al study, anesthesia was closed-loop controlled in 102 children ASA I-II where median (range) age and weights were 12.5(6-17) yr and 48(19-75) kg. The study was conducted in two stages. The originally tuned PID controller was evaluated in 31 cases. The acquired results were used to fine tune the final controller which was evaluated in 71 cases.

The controller performance at induction (0min < time < 20min) of anesthesia was evaluated based on overshoot, $S_{os}$ and with rise-time, $T_{ind}$. During maintenance (20min < time < 60min) of anesthesia, the performance of the MPC controller was assessed in terms of percentage error (PE)-based metrics commonly used in anesthesia closed-loop control systems [72]. The median PE (MDPE), median absolute PE (MDAPE), divergence and wobble were calculated using the maintenance portion of the procedure and are presented in Table 4.2 and Table 4.3. The sign of MDPE represents the direction of the PE, where a negative value indicates that the controller tends to overdose the patient, leading to depth of hypnosis levels below target, whereas a positive value show the tendency of a light anesthesia. MDAPE indicates the expected size of the error between the systems output and the set-point. Wobble measures the intra-patient variability in performance errors and divergence reflects the possible time-related trend of the output in relation to the set point. (PE)-based metrics were introduced to assess the performance of target controlled infusion (TCI) systems. These metrics are argued to be inadequate for evaluating EEG-guided automatic control of depth of
hypnosis [73] and are only employed in this preliminary study to provide a comparison of current results and those obtained by Hahn et al. and van Heusden et al.

<table>
<thead>
<tr>
<th>Gr</th>
<th>#</th>
<th>Controller</th>
<th>$S_{os%}$</th>
<th>$T_{ind}$</th>
<th>WAV CNS &lt;55 [%]</th>
<th>MDPE [%]</th>
<th>MDAPE [%]</th>
<th>Divergence [%/min]</th>
<th>Wobble [%]</th>
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<td>3.7±7.5</td>
<td>4.1±2.1</td>
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<td>0.9±0.8</td>
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<td>Hahn</td>
<td>14.3±9.8</td>
<td>5.2 ± 0.8</td>
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<td>-0.3±0.1</td>
<td>0.7±0.3</td>
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<td>0.6±0.2</td>
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<tr>
<td></td>
<td></td>
<td>Hahn</td>
<td>13.7±12.8</td>
<td>2.4±0.3</td>
<td>1.2±0.2</td>
<td>1.6±0.3</td>
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<td>0.6±0.2</td>
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<td>1.1±0.8</td>
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<td>2.0±5.0</td>
<td>5.3±1.3</td>
<td>0.5±0.3</td>
<td>2.6±0.7</td>
<td>-0.28±0.08</td>
<td>2.8±0.7</td>
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<th>$T_{ind}$</th>
<th>WAV CNS &lt;60 [%]</th>
<th>MDPE [%]</th>
<th>MDAPE [%]</th>
<th>Divergence [%/min]</th>
<th>Wobble [%]</th>
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<td>47</td>
<td>MPC$_{child}$</td>
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<td>50±5</td>
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<td>4.5±1.5</td>
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<td>71</td>
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<td>3.7±1.2</td>
<td>-6.2±5.3</td>
<td>8.8±4.2</td>
<td>N/A</td>
<td>6.0±2.4</td>
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Table 4.3: Performance of the MPC and the van Heusden et al controller [7] during induction and maintenance of simulated surgery in Children [62].
The MPC controllers presented in this study meet the overshoot specification stated in section 5.1. WAV\textsubscript{CNS} values below 40 are associated with occurrence of apnea\textsuperscript{7}, making the overshoot value a significant performance factor especially for the cases where spontaneous breathing is required. Pain on injection of propofol is another common concern particularly for pediatric anesthesiologists making the rise-time another important aspect in performance evaluation for closed-loop control of anesthesia. In the field of anesthesia, rise-time is commonly defined as the time that takes for depth of hypnosis index to fall below 60 and for the patient to be in a moderate hypnotic state. A WAV\textsubscript{CNS} index of 60 was reached with the MPC\textsubscript{adult} and MPC\textsubscript{child} controller within an average of 4.1 min and 5min respectively. The trade-off to guarantee stability given the large inter-patient variability is the slower than desired rise-time for insensitive patients.

Figure 4.7 and Figure 4.8 show the MPC closed-loop simulations for the 44 adult patients and 47 pediatric patients respectively. The results show that despite the large inter-patient variability in adults and especially in children, stability and performance is achieved.

4.9 Discussion

MPC is a control strategy that offers solutions for the regulation of constrained linear or nonlinear systems [56]. Robust MPC controllers are presented for closed-loop control of depth of hypnosis in adults and children. Uncertainty, due to inter-patient variability, is quantified with respect to an identified nominal patient model. Robustness in the presence of this patient variability is taken into account in the controller design. Evaluation of the proposed MPC controllers during simulated induction and maintenance of anesthesia show that the design specifications are met and that the required robustness against patient uncertainty is achieved.

In the field of anesthesia, an advantage of MPC is that it provides the ability to add constraints on drug infusion rates and predicted drug concentrations. A limitation of the proposed

\textsuperscript{7} Apnea: temporary cessation of breathing.
nominal model in this works is that the states no longer represent the hypothetical compartments of a traditional PKPD model (see 2.11 and 2.1.2) and therefore their corresponding values no longer embody drug concentrations at those compartments. This can be an issue when constraints are to be considered on predicted drug concentrations.
Figure 4.7: Closed-loop MPC$_{\text{adult}}$ control response of 44 patient models using WAV$_{\text{CNS}}$ index.
Figure 4.8: Closed-loop MPC\textsubscript{Child} control response of 47 patient models using WAV\textsubscript{CNS} index. For all patients, a hypothetical surgical stimulus is fixed to start 20min after the beginning of the simulation, (dotted line).
5. Safety Constraints for Model Predictive Control of Hypnosis

Safety bounds on estimated drug concentrations and magnitude of infusion rates have been included in a number of experimental systems for closed-loop control of anesthesia [25], [31]. van Heusden et al [31] investigated a number of scenarios encountered in anesthesia practice where there is an obvious need for safety. The constraints were defined based on the therapeutic window of propofol and were implemented in a PID closed-loop system with anti-windup [31]. A control system using an individualized MPC controller plus a ‘risk control’ supervisory system was employed by Sawaguchi et al [25] during a study of closed-loop control of hypnosis. The authors implemented the supervisory system to imitate counter measures taken by anesthesiologists for undesirable states such as intraoperative arousal, hypotension (low blood pressure), and bradycardia (heart rate under 60 beats per minute).
MPC offers solutions for the regulation of constrained linear or nonlinear systems [56]. In the field of anesthesia, MPC provides the ability to impose constraints on the magnitude and the rate of change of the input (infusion rate), the system states (drug concentrations) and the output (e.g., depth of hypnosis) as part of the control design. In the previous chapter, we presented the design of a robust unconstrained MPC of propofol in adults. The implemented MPC controller was shown via simulation to be robust to patient variability in the study population. The objectives of this chapter are i) to explore the importance of constraints in closed-loop control of hypnosis, ii) to add constraints to the previously designed and evaluated MPC system and iii) to assess the consequences of the constraints on the performance of the closed-loop control system in simulation. The main novelty is the use of auxiliary models for handling constraints on physiological parameters, exemplified by systolic blood pressure [74].

5.1 Safety Constraints for Hypnosis

Constraints on the amplitude of the control variable $u$, here the propofol infusion rate, are in part due to hard physical constraints on the system. The infusion rate can obviously not be negative, and maximum infusion rate can be enforced to minimize hemodynamic changes which usually follow a propofol infusion. Bilotta et al. showed in a study in which patients were randomly assigned to receive propofol at two different infusion rates (10mg/s vs 2mg/s), that the higher infusion rate induced a larger drop in mean arterial pressure than the lower infusion rate [75]. Having constraints on the magnitude of $u$ will give the option to limit the maximum rate. The infusion rate in this study is constrained between 0 and 600ml/hr, whereas the infusion pump is capable of a rate of up to 1200ml/hr.

$$0 \leq u(t) \leq 600\text{ml/hr}. \quad (5.1)$$

One of the main effects of propofol on the cardiovascular system is a decrease in arterial blood pressure due to a drop in systemic vascular resistance. Reductions in systolic blood pressure
(SBP) greater than 25% have been reported during induction of anesthesia with propofol [76]. West et al. [77] evaluated the intraoperative blood pressure measurements for 35 adults age 64.5 [38-81] yr, ASA I-III where propofol was closed-loop controlled and remifentanil was administered by target controlled infusion. Hypotension was treated in 7 (19%) subjects during the period between the start of propofol infusion and skin incision (start of surgery). Kazama et al. investigated the effect of age on SBP change with propofol in patients aged 20-85yr. Their results showed that at high plasma concentrations (>10 μg/ml), propofol may significantly decrease SBP, an effect more evident in elderly (> 70 yr) patients [76].

Another effect of high propofol concentration is a reduction of cerebral electrical activity as confirmed by an EEG Burst Suppression (BS) pattern with significant periods of isoelectric activity[78]. Besch et al. reported that the occurrence of isoelectric periods is more frequent with increasing hypnotic effect-site concentration, suggesting that BS may indicate too deep anesthesia [79]. Their study concluded that the main independent factors linked with BS were advanced age, medical history of coronary disease and male gender. The onset of BS has been reported with effect-site concentrations higher than 8 μg/ml, [78] without opioids and 7.3 μg/ml with an opioid (remifentanil 30 μg/kg/min) [80].

The lower bound on the propofol concentration is generally defined by awakening concentrations. Light anesthesia is a result of low propofol concentration and is associated with an increased possibility of awareness during surgery[81]. Propofol concentrations less than 1.6μg/ml (when administered with fentanyl) [82] and 1.8 μg/ml [83] without opioids are associated with awakening from anesthesia.

Safety bounds on the estimated propofol plasma concentration ($C_p$) and estimated effect-site concentration ($C_e$) can be defined using the therapeutic window for propofol as constraints on measured physiological parameters explained above. These bounds should be considered in the controller design:
Safety Constraints for Model Predictive Control of Hypnosis

\[ 1.6 \leq C_p \leq 10 \mu g/ml . \]  \hspace{1cm} (5.2)

\[ 1.6 \leq C_e \leq 7 \mu g/ml . \]  \hspace{1cm} (5.3)

One should note that those concentrations are calculated based on an open-loop population-based PKPD model and thus may not be a good indication of the actual concentrations for a given patient. This reinforces the need for introducing constraints on measured physiological parameters.

### 5.2 Constrained Closed-loop Control of Hypnosis

#### 5.2.1 Controller Design

Figure 5.1 (a) shows the setup for the constrained closed-loop control of hypnosis. The patient response is measured by the NeuroSENSE Monitor. The controller uses the set-point defined by the anesthesiologist and the measurement from the DOH monitor to calculate the next optimized propofol infusion rate (4.3). The nominal model, \( G_o \), to be used for the controller, is constructed from individual frequency responses of 44 subjects (4.1) as presented in Section 4.3. Because of the technique that is used in the construction of \( G_o \), the states do not represent the hypothetical PK compartments. To predict the propofol concentration in the central compartment and at the effect-site and compare them against the concentration constraints, a 4-compartment PKPD model (a 3 compartment PK model plus an effect-site compartment) is used in parallel with the patient model, Figure 5.1 (b). The 4-compartment PKPD model is represented in state-space as follows:

\[
\begin{bmatrix}
    \dot{x}_1 \\
    \dot{x}_2 \\
    \dot{x}_3 \\
    \dot{x}_4
\end{bmatrix} =
\begin{bmatrix}
    -(k_{i0} + k_{i2} + k_{i3} + k_{e0}) & k_{i2} & k_{i3} & k_{e0} \\
    k_{21} & -k_{21} & 0 & 0 \\
    k_{31} & 0 & -k_{31} & 0 \\
    k_{e0} & 0 & 0 & -k_{e0}
\end{bmatrix}
\begin{bmatrix}
    x_1 \\
    x_2 \\
    x_3 \\
    x_4
\end{bmatrix} +
\begin{bmatrix}
    1 \\
    0 \\
    0 \\
    0
\end{bmatrix} u . \hspace{1cm} (5.4)
\]
where $k_{10}$ is the elimination rate, $k_{ij}$ is the distribution rate constant from compartment $i$ to $j$. $x_1$ represents the amount of drug in the central compartment, $C_p$, and $x_4$ represents the amount of drug in the effect-site compartment, $C_e$.

\[\text{MPC Controller} \rightarrow \text{Patient Model} \rightarrow \text{DOH Monitor} \rightarrow \text{DOH Index}\]

\[(a)\]

\[\text{MPC Controller} \rightarrow \text{Patient Model} \rightarrow \text{DOH Monitor} \rightarrow \text{DOH Index}\]

\[(b)\]

\[\text{MPC Controller} \rightarrow \text{Patient Model} \rightarrow \text{DOH Monitor} \rightarrow \text{DOH Index}\]

\[(c)\]

Figure 5.1: The MPC closed-loop system, a) with no constraints or only constraints on the infusion rate, b) with an auxiliary 4-compartment PKPD model to predict concentrations for an MPC with constraints on plasma concentration and effect-site concentration, c) with an auxiliary BP Model to predict systolic blood pressure for an MPC with constraint on BP.
At the start of a propofol infusion, after an increase in the infusion rate or after a bolus, the concentration of drug in the plasma first rises. Then, the concentration at the effect-site compartment increases until the maximum effect-site drug concentration is reached. When simulating this process, \( C_p \) should be allowed to have a greater initial concentration limit than \( C_e \). After \( C_e \) has reached its steady-state concentration, \( C_{p\text{max}} \) should be set equal to \( C_{e\text{max}} \). This way, after the initial spike in \( C_p \), the concentration constraint is modified (reduces) as the concentration in \( C_e \) increases. When the infusion is stopped or the infusion rate is reduced, the concentration of propofol in the central compartment falls first, the minimum concentration reached by \( C_p \) may be lower than \( C_e \). This is shown in Figure 5.2.

Figure 5.2: Infusion rate and predicted plasma concentration (solid line) and effect-site concentration (dashed line) for patient #8 in the presence of disturbance from minute 20–45.
5.2.2 Effect-Site Concentration (Depth of Hypnosis as Clinical End-Point)

To predict $C_e$, (5.4) is evaluated as explained in [36] with $k_e (18-60\text{yr}: 0.456 \text{ min}^{-1})$. The $C_e$ constraint is written as follows:

$$C_{e_{\text{min}}} \leq C_e \leq C_{e_{\text{max}}}$$  \hspace{1cm} (5.5)

$$C_{e_{\text{min}}} \leq \frac{[0 \ 0 \ 0 \ 1]}{C_p}\cdot (Ax[k] + Bu[k]) \leq C_{e_{\text{max}}}.$$

To be compatible with the control algorithm (4.2), the constraints are rearranged in terms of $\Delta u$:

$$C_e \leq C_{e_{\text{max}}}$$
$$\Rightarrow C_{\text{effect}} \cdot B\Delta u[k] \leq C_{e_{\text{max}}} - \frac{C_{\text{effect}} \cdot (Ax[k] + B[u[k-1]])}{h_{Ce}}$$ \hspace{1cm} (5.6)

$$C_{e_{\text{min}}} \leq C_e$$
$$\Rightarrow C_{e_{\text{min}}} - \frac{C_{\text{effect}} \cdot (Ax[k] + B[u[k-1]])}{h_{Ce}} \leq C_{\text{effect}} \cdot B\Delta u[k]$$

Following the same guidelines as those explained for $C_e$, (5.5) and (5.6) the constraints for $C_p$ can be written as follows:

$$C_{p_{\text{min}}} \leq \frac{[1 \ 0 \ 0 \ 0]}{C_{p_{\text{max}}}}\cdot (Ax[k] + Bu[k]) \leq C_{p_{\text{max}}}$$ \hspace{1cm} (5.7)

As explained before, the maximum and minimum limits for $C_p$ can change. From the values suggested in (5.2) and (5.3), we have:

$$C_{p_{\text{max}}} = \min \left[ \frac{10}{7 + (7 - \Delta Ce)} \right]$$

$$C_{p_{\text{min}}} = \max \left[ \frac{1.6}{1.6 + (1.6 - \Delta Ce)} \right]$$ \hspace{1cm} (5.8)
5.2.3 **Blood Pressure (SBP as Clinical End-Point)**

An optional but important constraint to be considered in closed-loop control of hypnosis is the maximum drop in SBP during induction of anesthesia. Kazama et al [76] showed that the effect of propofol on the BIS depth of hypnosis monitor occurs more rapidly compared with the effect on SBP. To predict $C_{SBP}$, (5.4) is calculated using the PK model [36] in parallel with the patient model and $k_{e0}$ (20-39yr: 0.1232 min$^{-1}$, 40-59yr: 0.1182 min$^{-1}$ and 60-69yr: 0.0778 min$^{-1}$) identified in [76]. Kazama et al expressed the effect of propofol on SBP as the percent SBP decrease from baseline, $SBP_{base}$ to 80mmHg as follows:

$$SBP_{\%} = \frac{SBP - 80}{SBP_{base} - 80} \times 100 = 100 - 100 \frac{Ce_{prop}[k]}{EC_{50} + Ce_{prop}[k]}, \quad (5.9)$$

where $EC_{50}$ is the propofol concentration associated with the 50% of maximum effect and $\gamma$ is the Hill coefficient.

To limit the lower bound on SBP, by optimizing w.r.t. $\Delta u$, a linear relationship has to be established between SBP and the effect-site concentration. The Hill equation in (5.9) was linearized around the point at which the SBP decreases from the baseline to the 50% point (i.e, a 50% decrease from baseline to 80mmHg) with a constant slope of unity.

$$SBP_{\%} = 100 \frac{Ce_{prop}[k]}{2EC_{50}}, \quad (5.10)$$

Surgical stimulations such as insertion of laryngeal mask airway\(^8\) result in cardiorespiratory changes such as an increase in blood-pressure. The current SBP model cannot account for the effect of external stimulations and is best used to predict the initial drop in SBP during induction of anesthesia. The effect of propofol on SBP in adults was simulated by combining the Schnider PK Model [36] and

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\(^8\) Laryngeal mask airway is a medical device that keeps a patient's airway open during anesthesia
the blood pressure PD model by Kazama et al [76], also Figure 5.1 (b). The resulting PKPD model was evaluated on clinical data collected during a previously reported study where 36 adults ASA I-III, age 38-82 years and body mass index of 17.9-35.8, adults, undergoing surgery requiring general anesthesia were enrolled [77]. Figures 5.3 and 5.4 present the result of predicted SBP profile compared with the measured noninvasive blood pressure collected during closed-loop control of anesthesia for patient #3 and patient #8. In this work, hypotension is defined as a SBP drop of 50% from the baseline to 80mmHg, using the equation (5.9).

In the current implementation, we predicted the SBP value using the model by Kazama et al [76]. But for the future-work and when measured blood pressure values are available, the model can be modified to incorporate and use the measured blood pressure value, Figure 5.1 (c). A Kalman filter in such implementation can be used to estimate the subsequent blood pressure concentration and predict the output based on the new infusion rate.

### 5.3 Optimization

The control objective is to minimize a performance index, $J$ involving the difference between the set-point $r(k)$ and the predicted output $y(k)$ within a prediction horizon:

$$J = \sum_{k=0}^{n_p} \| y(k) - r(k) \|^2_Q + \sum_{k=n_c}^{n_p} \| \Delta u(k) \|^2_R,$$

subject to:

- $0 \leq u(k) \leq 600 \text{ ml/hr}$
- $1.6 \leq C_r(k) \leq 10 \mu g/\text{ ml}$
- $1.6 \leq C_u(k) \leq 7 \mu g/\text{ m}$ or $\text{SBP}_{\text{max}} \leq 50$

where $n_c$, the control horizon, is the number of samples used to capture the future control trajectory and $n_p$, the prediction horizon is the length of the optimization window, while $Q$ and $R$ are weights on the output error and incremental input respectively.
Figure 5.3: Recorded a) $\text{WAV}_{\text{CNS}}$ and propofol infusion profile, and b) top: noninvasive systolic blood pressure (black solid line) and predicted systolic pressure (red dotted line) for patient #3 during a closed-loop control of anesthesia. Start of airway insertion and procedure are marked with blue and green vertical lines respectively, bottom: predicted $C_p$ (red line) and $BP\ Ce$ (blue line), where $BP\ Ce$ is the effect-site concentration when SBP is the clinical end-point.
Figure 5.4: Recorded a) WAV_{cns} and propofol infusion profile, and b) top: noninvasive systolic blood pressure (black solid line) and predicted systolic pressure (red dotted line) for patient #8 during a closed-loop control of anesthesia. Start of airway insertion and procedure are marked with blue and green vertical lines respectively, bottom: predicted C_p (red line) and BP Ce (blue line), where BP Ce is the effect-site concentration when SBP is the clinical end-point.
The function $J$ and the constraints (5.11) can be written in another form:

$$J = \min_{\Delta U} \frac{1}{2} \Delta U^T H \Delta U + \Delta U^T f,$$

subject to $M \Delta U \leq \Gamma$.

where $M$ represents the constraints. The number of rows in the matrix $M$ is equal to the number of constraints and the number of columns is equal to the dimension of $\Delta U$.

The inequality constraints may consist of active constraints and inactive constraints. The Kuhn-Tucker conditions define the active and inactive constraints in terms of the Lagrange multipliers, $\lambda$. For an active constraint, the resultant $\lambda$ is positive and for a non-active constraint, $\lambda$ equals zero [84]. Here we use the dual active method, Hildreth’s quadratic programming procedure [20] to systematically identify the constraints that are not active. The dual problem to the original quadratic problem is given by $J$ where $H = ME^{-1}M$ and $K = \gamma + ME^{-1}F$:

$$J = \frac{1}{2} \lambda^T H \lambda + \lambda^T K + \frac{1}{2} \gamma^T E^{-1} \gamma$$

subject to $\lambda \geq 0$.

(5.13)

Let the optimal solution of this quadratic program be given by $\lambda^*$. Using Hildreth’s algorithm, $\lambda^*$ can be obtained with successive optimization of each element of $\lambda$ separately, where $h_{ij}$ is the $ij$th element in $H$ and $k_i$ is the $i$th element in $K$.

$$\lambda_i^{m+1} = \max(0, \omega_i^{m+1})$$

$$\omega_i^{m+1} = -\frac{1}{h_{ii}} \left[ k_i + \sum_{j=1}^{i-1} h_{ij} \lambda_j^{m+1} + \sum_{j=i+1}^{m} h_{ij} \lambda_j^n \right],$$

(5.14)

The algorithm of Hildreth is simple and does not involve matrix inversion. In the event of conflict between constraints, the algorithm will deliver a compromise without terminating. Due to the hard physical constraints on the pump, the system is unable to deliver a negative infusion or have an infusion rate greater than the maximum infusion rate possible with the propofol pump. To simulate a
real surgical environment, hard constraints on the infusion rate were also implemented in the system (a second constraint limits the infusion rate, \( u \) between zero and the maximum infusion rate, 600ml/hr). For the current system, the following parameters were considered \( n_p = 60, n_c = 2, R_w = 1, R_v = 9, R = 0.8 \). The details of tuning procedure are explained in the previous chapter.

### 5.4 Monte Carlo Simulations

Analytically proving the robustness of the proposed control system in presence of constraints is complicated. For the purpose of this study, Monte Carlo simulations were used to observe the robustness[85]. Eight hundred and eighty random models were created by applying ±20% perturbations to all the PK and PD parameters of the patients in the study and generating 20 random models for each of the 44 individuals. The number of samples was determined by trial and error. We used 10, 20, and 30 Monte-Carlo models (for each of the 44 individuals) in simulating surgery scenarios. The results using 20 and 30 Monte-Carlo models were very close to each other and consistent upon repeating the simulation. To minimize the computation time while keeping the reliability of the results, we settled on 20 Monte-Carlo models per individual.

### 5.5 Results

Simulated induction of anesthesia was completed in an average (SD) of 3.4(2.0) min with set-point overshoot (WAV\textsubscript{CNS} <50) of 2.7%(6.1) for the constrained MPC. Comparing those results with the ones obtained with the unconstrained MPC, (induction time 2.9(0.9) min and overshoot of 3.7%(7.5) suggests that safety constraints can be added to the control system for hypnosis without significantly increasing the rise time, Table 5.1.

Results obtained with an unconstrained MPC emphasize the importance of the concentration constraints, as they show that without them, 39% of patients would reach \( C_p >10 \) µg/ml and 36% of
patients would reach $C_e > 7 \mu g/ml$, Figure 5.5 and Figure 5.6. These high concentrations may result in significant drops in SBP and may also increase the incidence of BS as was discussed in Section 5.2.

<table>
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<th>MPC Controller</th>
<th>Rise-Time [min]</th>
<th>Overshoot [%]</th>
</tr>
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<td>Unconstrained</td>
<td>2.9±0.9</td>
<td>3.7±7.5</td>
</tr>
<tr>
<td>Constrained (1.6≤ $C_p$≤10 μg/ml &amp; 1.6≤ $C_e$≤7 μg/ml)</td>
<td>3.4±2.0</td>
<td>2.7±6.1</td>
</tr>
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</table>

Table 5.1: Rise-Times is defined as time in minutes required for WAV CNS to fall below 60 and Overshoot as the percentage of WAV CNS index below the set-point of 50 [74].

Figure 5.7 shows the results of Monte Carlo simulations for 880 random patient models. The control system is shown to be robust with the ±20% uncertainties to the PK and PD parameters and in the presence of simulated disturbance. The ±20% uncertainties resulted in numerous patients which are far from the average population and are considered outliers. These were patients with very long delays, very slow or very fast clearance, etc. When coming across such cases, often identified during induction of anesthesia, anesthesiologists may modify set-point and constraint values, which in return should improve the performance. A few cases were encountered while running the Monte Carlo simulations, where due to conflict between constraints; Hildreth’s QP was forced to deliver a compromised solution. Compromise on the infusion rate constraint could mean a value outside the physical limit of the pump, which as explained before was restricted by adding the extra hard constraint to the system. Figure 5.8 shows an example of this case.

Figure 5.9 shows the results of the SBP constraint on the closed-loop MPC response with no disturbance. It further shows the percent SBP drop from baseline to 80 mmHg with BSP constrained MPC and unconstrained MPC respectively. The implemented constraint is effective in controlling the SBP above the limit. This is achieved as a trade-off to a slower induction.
Figure 5.5: Closed-loop MPC response of 44 patients with unconstrained MPC.
Figure 5.6: Closed-loop MPC response of 44 patients with constraints on $C_p$ ($1.6 \leq C_p \leq 10 \, \mu g/ml$) and $C_e$ ($1.6 \leq C_e \leq 7 \, \mu g/ml$).
Figure 5.7: Closed-loop MPC response of 880 Monte Carlo simulated patients with constraints on $C_p$ ($1.6 \leq C_p \leq 10 \, \mu\text{g/ml}$) and $C_e$ ($1.6 \leq C_e \leq 7 \, \mu\text{g/ml}$).
Figure 5.8: Closed-loop MPC response for patient #155 where a conflict between constraints, $u$ (infusion rate) $<600$ ml/hr and $C_p > 1.6$ resulted in a compromised solution. The resulting $u$ around 37min was restrained with the hard constraint.

Figure 5.9: Top) Closed-loop MPC response of 44 patients with SBP limit of 50%. Percent SBP drop in from baseline to 80mmHg in, bottom left) constrained, bottom right) unconstrained.
5.6 Discussion

The contributions of this chapter are threefold: 1) the importance of safety constraints in closed-loop control of hypnosis with propofol is explored, 2) A novel idea is introduced on how to define and implement physiological constraints in closed-loop control of hypnosis using MPC with a parallel PKPD model, 3) Robustness of the closed-loop system with respect to patient variability is investigated and confirmed via Monte Carlo simulations. Evaluation of the proposed MPC controller during simulated induction and maintenance of anesthesia shows that the design specifications are satisfied. The proposed constrained control strategy can potentially reduce the risk of under- or overdosing for most patients by providing controller enforced safety bounds.

Incorporating the safety constraints in the controller will reduce the risk of under or overdosing for the majority of patients. But there are patients that will reach the defined safety bounds because their required drug dose or response to the drug is very different from the population average. Also in the presence of surgical stimuli patients may tolerate higher propofol concentrations without experiencing serious cardiovascular side-effects. Due to these situations and influences, the values selected as safety bounds in this study are only guidelines. Adjustments to these values should be made by the anesthesiologist to factor in age, ASA status, known medical history, opioids use, intensity of expected stimuli, etc.

An MPC design with constraint on SBP during induction of anesthesia with propofol was investigated. The importance of constraint on systolic blood pressure can be seen from many studies in literature. Recent studies have shown that anesthesia incidents of low mean arterial blood pressure and deep hypnotic levels may be linked with complications and postoperative mortality[86]. Those scenarios may be more pronounced in the elderly or patients undergoing cardiac surgery. There are limitations with the current SBP auxiliary model. The clinical data used for this investigation were not primarily collected for the purpose of a blood pressure study and do not include the baseline SBP value and measured blood pressure values. The SBP model proposed by Kazama [76], has been identified
on a very limited number of patients, as compared to PK models derived involving hundreds of subjects.

It should be remembered that opioids reduce the amount of propofol required, causing greater clinical effects than would be expected with propofol alone [87]. From a control point of view, it is important to account for the synergic effect between hypnotics and analgesic drugs. Current models in the literature that explain the synergic effect only tend to describe the drug interaction in steady-state and fail to characterize the dynamics related to transitory events. The goal of this chapter was to study the need for the constraints in the application of closed-loop control of hypnosis and also to demonstrate the simplicity of their implementation in a closed-loop MPC of hypnosis rather than defining clinical bounds.
6. Conclusions and Contributions

In the field of anesthesia a significant reason to close the loop and use feedback is that it reduces the sensitivity to disturbance and effect of uncertainty. However, the challenge is now finding the appropriate compromise between performance and robustness[88]. With such properly designed and implemented closed-loop system in anesthesia, the anesthesiologists are then free to focus on higher-level clinical tasks and decisions. Automated control systems in anesthesia have the potential to improve patient safety.

This concluding chapter reviews the work done under this Ph.D. program, emphasizing in particular the significance and contributions of this thesis. New research directions are also proposed, to further this work towards the development of a closed-loop system suitable for the everyday practice of clinical anesthesia in the operating room.
6.1 Synopsis

Chapter 2 provided a background on PK and PD concept and mathematical representation for propofol models. PK models used for TCI of propofol frequently employ an effect site equilibration rate constant, $k_{e0}$ that is derived from adult studies. PD differences between adults and children, however, dictate that it is unacceptable to extrapolate available adult PD data to pediatric models. Although pediatric PK data on intravenous anesthetics are available, the availability of pediatric PD data is relatively limited. Previous pediatric PD studies investigating propofol administration in children have described PD models based on the BIS index and AEP monitors. In this work we have identified a pediatric PD model of propofol in children, based on the SE, NeuroSENSE, and respiratory responses as clinical end-points of interest. The identified model with NeuroSENSE was compared with PD models identified with same monitor but specifically for the design of a robust linear closed-loop controller. Comparing parameters of different PD models, it is clearly indicated that the parameters, specifically $k_{e0}$ estimated using a particular monitor is not acceptable for use in studies with different monitors.

Chapter 3 presents a new monitor-decoupled model of propofol PD model using the SE index as the clinical endpoint of interest. In our model, the dynamics of the Entropy monitor are separated from the PD response of the patient by explicitly accounting for the model of the Entropy monitor in the PD identification process. The monitor model was then excluded from the identified PD model for the patient. The PD model thus obtained is distinct from its traditional counterpart (two-stage) in that it reflects the PD response of a patient with the dynamic effects of the monitor included as a specific entity. System identification trials using SE data of 31 pediatric subjects show that the PD models derived from the proposed approach are an improvement on the traditional approach. For the Paedfusor pharmacokinetic (PK) model, population-averaged effect site equilibration rate constant ($k_{e0}$) was 5.4 and 3.0 for the proposed and traditional PD models ($p<0.001$), respectively. For the Kataria PK model, population-averaged $k_{e0}$ was 2.3 and 1.4 ($p<0.01$). This significant difference suggests that the effects
of the monitor must be considered when searching for the intrinsic PD of a patient that is free from the bias induced by the monitor characteristics.

In chapter 4, the design of an MPC controller that includes robustness in the design step is presented for control of depth of hypnosis in adults and children. The control strategy is designed to overcome the large inter-patient variability in response to a standardized anesthetic drug infusion using robust control principles. A nominal model is constructed from individual frequency responses of patient models. To reduce the uncertainty, the parameters of the nominal model are tuned by minimizing the difference between the nominal and individual patient models in the frequency domain. The uncertainty with respect to this nominal model is then quantified. The effect of the tunable controller parameters on stability and performance is investigated by using sensitivity functions. For each population, the performance of the MPC controller on a set of models is assessed in simulation during induction and maintenance of anesthesia including surgical stimulation. Evaluation of the proposed MPC controller meets the design specifications and shows that the required robustness against patient uncertainty is achieved.

Chapter 5 explores the importance of safety constraints in closed-loop control of propofol in adults. A constrained model predictive controller is introduced and implemented for closed-loop control of hypnosis. Safety bounds on estimated propofol concentrations, magnitude of infusion rate and systolic blood pressure are considered. Robustness of the closed-loop system with respect to patient variability is investigated and evaluated via Monte Carlo simulations. Results show that the proposed constrained control strategy can potentially reduce the risk of under- or overdosing for most patients by providing controller enforced safety bounds without sacrificing the performance of the closed-loop control system.
6.2 Significance

The main contributions and implications of this thesis are summarized below:

I. A two-stage approach for pharmacodynamic parameter identification is presented.

Pediatric pharmacodynamic models are derived using the two-stage approach and with different monitors to measure the clinical effect. The method and the identified models are compared with those in literature. Due to its relative computational efficiency, the two-stage approach demonstrates to be an attractive alternative to PD modeling approach in situations where data are not sparse.

II. A monitor-decoupled approach is presented for pharmacodynamics Modeling.

A monitor-decoupled PD model is presented that describes the anesthetic effect of propofol in children using the SE as the clinical end point. The presented model decouples the dynamic delay introduced by the monitor and significantly increases the $k_{e0}$, which predicts a more rapid clinical effect but does not change the other model parameters. The results suggest that it may be beneficial to explicitly consider the effects of the monitor dynamics when identifying a PD model.

III. PKPD Uncertainty is identified for adults and pediatric population and is incorporated as part of MPC robust tuning.

Robust MPC controllers are presented for closed-loop control of depth of hypnosis in adults and children. Uncertainty, due to inter-patient variability, is quantified with respect to an identified nominal patient model. Robustness in the presence of this patient variability is taken into account in the controller design. Evaluation of the proposed MPC controllers during simulated induction and maintenance of anesthesia show that the design specifications are met and that the required robustness against patient uncertainty is achieved.

IV. A novel idea is introduced on how to define and implement physiological constraints in closed-loop control of hypnosis using MPC with a parallel PKPD model.
The importance of safety constraints in closed-loop control of hypnosis with propofol is explored and robustness of the closed-loop system with respect to patient variability is investigated and approved via Monte Carlo simulations. Evaluation of the proposed MPC controller during simulated induction and maintenance of anesthesia shows that the design specifications are satisfied. The proposed constrained control strategy can potentially reduce the risk of under- or overdosing for most patients by providing controller enforced safety bounds.

6.3 Future Work

We propose here some directions for future research and development work.

6.3.1 New Pharmacodynamic Models

The clinical studies described in chapter 2, were not primarily designed for the purpose of PD model identification, and some aspects of the experimental protocol were not optimally designed for this purpose. While we showed that approximate models, that are sufficiently accurate for control, can be identified from those clinical data, it would be recommended to design and conduct clinical studies for the sole purpose of PD models identification. Identification or use of a burst suppression model and use of the respiratory model as identified in chapter 2 as auxiliary models for incorporating related constraints could also be investigated.

When designing a new clinical study for PD identification, the number of cases in the study and in each age group should be sufficient to reach a statistically representative result. The 44 adults model set used in this work included very few cases in the 40-49 and 50-60 yrs age groups and none over the age of 60. Also the 52 pediatric model sets used here, did not include children under the age of 6.

Identifying a new or better validation of the current SBP model is also needed. Our clinical studies were not designed for this purpose and the blood pressure data for many patients was missing sections or did not include preoperative baseline value. Also as mentioned in Chapter 5, in the current
MPC system with SBP constraints, the SBP value is predicted using the model by Kazama et al [76]. In future work and when measured blood pressure values are available, the model may be modified to incorporate the measured blood pressure value. With real-time blood pressure data available, a Kalman filter can be used to estimate the subsequent blood pressure concentration and predict the output based on the optimized infusion rate.

6.3.2 Nociception Monitor

A real-time nociception monitor would increase patient safety during general anesthesia by ensuring that the patient receives the precise drug dose based on his/her level of surgical stress and physiology. Researchers from our group have been working on a novel real-time cardiorespiratory coherence (CRC) algorithm to monitor nociception during general anesthesia [89]. A nociception index was created from 0 (no nociception) to 100 (strong nociception). Upon completion of the nociception monitor development, a MIMO control law targeting both indexes may be derived.

6.3.3 MIMO System

The control of hypnosis alone will not provide anesthesiologists with the full advantages of automation. Controlling anesthesia implies the control of hypnosis, analgesia and paralysis. Paralysis can be viewed as a separate issue, but the control of hypnosis and analgesia must be approached within a multivariate framework to account for the synergic effect between the two drugs. An analgesia index will allow for a MIMO control law, targeting both depth of hypnosis and analgesia. The real benefits of MPC control will only become attractive on multivariable applications. This includes extending the proposed control design to multivariable control of hypnosis and analgesia before proceeding to clinical trials. The robust closed-loop control algorithm should be validated on clinical data. A prospective study could provide a solid assessment of closed-loop control algorithm performance.
Bibliography


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