Identifiability of pharmacological models from data

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Abstract

In order to automate anaesthesia in patients using propofol, closed-loop control systems with models that describe the time course of the drug effects on the body are required, usually being represented by pharmacokinetics and pharmacodynamics (PKPD). This thesis focused on evaluating parameter identifiability for the PK part of the model, using a model proposed by Eleveld et al. that has six parameters. Different sets of data were simulated with said model and Gaussian noise was added. To identify the parameters in the simulated data, Markov Chain Monte Carlo with the Metropolis-Hastings algorithm was applied for a set of different test cases. The results show that the estimations are dependent on the choice of priors and that the system is not uniquely identifiable. Although the estimated values differed from the parameters which were used for simulating data, the estimated parameters were able to fit the observed data very well in all trials. The conclusion of this work is that a PKPD model structure using six parameters is not practically identifiable and suggestions for future work would be to investigate whether a structure with fewer parameters could be more suitable for closed-loop control systems in anaesthesia.

Acknowledgements

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Finally, I would like to show courtesy to my family, who has provided me with support and encouragement throughout all my studies. Special gratitude is directed at my father who has been a great advocate for education, and who inspired me to pursue engineering.

Contents

1

Background

1.1 Introduction

To facilitate serious operational procedures for surgeons, as well as prevent pain and discomfort for the person undergoing the operation, general anaesthesia is induced in the patient. Anaesthesia means loss of sensation and amounts to safely and reversibly put the patient in an unconscious state [NHS, 2018].

Non-invasive continuous measuring systems, along with in-depth knowledge about drug effects on the human body, enable anaesthesiologists to manually administer drugs, observe the responses and adjust the doses accordingly. However, automating drug administration may contribute to a series of advantages in regards to patient safety and healthcare cost reductions [Jing and Syafiie, 2020].

In order to accomplish automation, closed-loop control systems with models that describe the time course of the drug effects are required, most commonly represented by pharmacokinetics and pharmacodynamics (PKPD). Pharmacokinetics describe how the body affects the induced drug, whereas pharmacodynamics describe how the drug affects the body [Soltesz et al., 2020].

Implementing closed-loop control systems comes with multiple challenges, and among those are model uncertainties [Jing and Syafiie, 2020]. The aim of this work was to provide further insight on the performance of a recently proposed model by Eleveld et al., which was developed for drug effect prediction for a broad population [Eleveld et al., 2018].

1.2 Anaesthesia

General anaesthesia is a reversibly induced state which causes loss of consciousness through hypnosis[1], amnesia[2], analgesia[3], and reduces the effect of reflexes of

[1] Hypnosis: a state of altered consciousness.
[2] Amnesia: loss of memories.
[3] Analgesia: loss of sensation of pain.

the autonomic nervous system[4]. The main goal is for the patient that undergoes general anaesthesia to be unable to process the information of the environment, as well as have no recollection of the events that occurred during the procedure. This includes physically painful events as well as experiences that may cause psychological trauma [Cascella, 2020b].

The induction of anaesthesia is conducted through a bolus dose[5], that puts the patient in the desired unconscious state. This is usually followed by constant rate infusions of the chosen drug or drugs. Once anaesthesia is reached, the forthcoming phase is maintenance. The maintenance phase aims to prolong the anaesthetic state in order for the intended procedure to be carried out successfully. Lastly, the ending stage, emergence, will be reached and it is characterized by the transition from unconsciousness to wakefulness [Soltesz, 2013].

The depth of anaesthesia (DoA) can be evaluated by measuring brain activity through a processed electroencephalogram (pEEG). One of the more commonly used non-invasive monitors in anaesthesia is the BIS monitor (Bispectral Index™ (BIS™), Medtronic, UK). It consists of a single adhesive sensor, placed on the patient's forehead, which collects EEG data. Once the signal has been processed, the system outputs a dimensionless number, referred to as the BIS-index. This index represents the DoA and ranges from 0, meaning there is no EEG signal, to 100, which represents a fully conscious patient. Values between 40-60 are appropriate levels of general anaesthesia and are hence suitable during the maintenance phase [Cascella, 2020a].

In current standard practice, an anaesthesiologist induces the desired state of unconsciousness in the patient and thereafter monitors it. However, automating drug administration may contribute to a series of advantages in regards to patient safety and healthcare cost reductions [Jing and Syafiie, 2020]. Furthermore, it shifts the focus of the anaesthesiologist to clinical events as opposed to monitoring and regulating the process [Soltesz, 2013].

Drugs used in anaesthesia are administered through injection or inhalation. The most common anaesthetics that are administered through injection are propofol, etomidate, midazolam, thiopental and ketamine. Inhaled drugs used in anaesthesia are halothane, desflurane, isoflurane, sevoflurande, nitrous oxide and xenon. Since these medications have small, uncharged molecules, they can cross the blood-brain barrier, giving the desired unconscious effect during surgery [Cascella, 2020a]. Remifentanil is an opioid[6] that is available for clinical use in anaesthesia in order to block noxious stimuli[7]. The drug assures deep intra-operative analgesia and assures safe and stable hemodynamics[8] during the procedure, without compromising on the

[4] Autonomic nervous system: the part of the nervous system that unconsciously controls and regulates bodily functions.

[5] Bolus dose: a dose given intravenously at a controlled, rapid rate.

[6] Opioids: drugs used to reduce pain.

[7] Noxious stimulus: an actually or potentially tissue damaging event.

[8] Hemodynamics: the study of blood flow and circulation.

desire of rapid awakening post operation. Another advantage of remifentanil is that it enables pharmacokinetic predictions [Komatsu et al., 2007].

1.3 Model structures

To automate the process of anaesthesia through closed-loop control systems[9], models are required that describe the mechanisms from the intravenous bolus dose and continuous infusion to the displayed signal on a BIS monitor. The following chapter introduces the reader to different model structures used in anaesthesia.

PKPD model structure

The traditional approach to model anaesthesia is achieved by using a pharmacokinetic pharmacodynamic (PKPD) model. Pharmacokinetics (PK) describe how the body handles the administered drug whereas pharmacodynamics (PD) describe the course in which the drug affects the body.

In order to receive an output of the model in terms of a BIS-number, the drug concentration in the body needs to be modelled. The final concentration of interest in this case is the effect site concentration, which is the concentration of the drug located in the brain, where the EEG activity is measured. If anaesthesia is induced intravenously or by inhalation, the goal is to describe the time course in which the drug travels throughout the body and eventually acts on the brain before it loses its effect. Modelling this process starts with pharmacokinetics and is followed by pharmacodynamics.

Pharmacokinetics Pharmacokinetics when using propofol is modelled by three compartments. A compartment is a homogeneous entity that specifies a state of a distributed substance. The three compartments that are constructing the pharmacokinetic structure exchange material with each other through transfer rate constants [Swietaszczyk and Jødal, 2019].

An alternative way of modelling pharmacokinetics is through physiological models that take all organ volumes and clearances[10] into account, creating an anatomically accurate description of how drugs distribute in the body over time. However, this approach seems to be unnecessarily complicated since it has not shown any superiority to the compartmental modelling. Hence, the compartment model structure has taken the lead as the most commonly used PK describer.

Pharmacokinetics are linked to the concentration of the drug in the plasma. This concentration is represented by the main compartment, Compartment 1 in Figure 1.1. From the main compartment, the rapid peripheral compartment (Compartment 2), and the slow peripheral compartment (Compartment 3) are connected through

[9] Closed-loop control system: a type of control system in which the controlling action shows dependency on the generated output of the system

[10] Clearance: the elimination of a substance from the body or other biological system.

drug transfer rate constants k_{ij} that go from compartment i to j. Constants k_{10} and k_{e0} are elimination rate constants [Jing and Syafiie, 2020]. The main compartment corresponds to the blood plasma, the rapid peripheral compartment represents the organs where the drug effect is instantaneous, such as heart and liver, and the slow peripheral compartment describes the drug distribution in organs where the effect is slower, such as fat and skeletal muscle [Savoca and Manca, 2020].

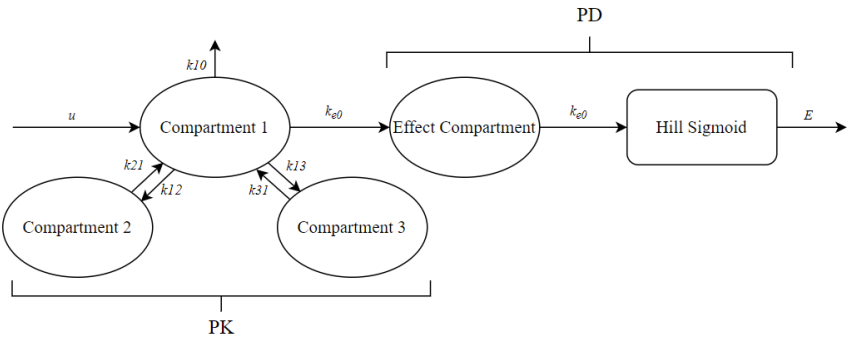

Figure 1.1 The traditional PKPD model structure, containing three compartments (PK), an effect compartment that accounts to the time lag between the drug effect in the blood plasma and the effect site, and a Hill function which outputs the BIS-numbers (PD).

With the aim to obtain the plasma drug concentration over time, the compartment models can mathematically be described by solving for C_1 in (1.1).

$$\begin{aligned} \dot{C}_1 &= -(k_{10}+k_{12}+k_{13})C_1 + k_{21}C_2 + k_{31}C_3 + \frac{1}{V_1}u \\ \dot{C}_2 &= k_{12}C_1 - k_{21}C_2 \\ \dot{C}_3 &= k_{13}C_1 - k_{31}C_3 \end{aligned} \tag{1.1}$$

where $\dot{C}_1, \dot{C}_2$ and $\dot{C}_3$ are the derivatives of the respective compartment concentrations over time, k_{ij} are the drug transfer rate constants, k_{10} is the elimination rate constant, V_1 is the volume of Compartment 1 and u is the input, which in this case is the drug dose [Jing and Syafiie, 2020].

Pharmacodynamics From the point when the drug is administered into the body until there is an observed effect on the brain, a time lag occurs. Therefore, another compartment that takes this lag into account is added (Effect Compartment), see Figure 1.1. The effect compartment is described by a first order differential equation

$$\dot{C}_e = k_{e0}(C_1 - C_e) \tag{1.2}$$

where $\dot{C}_e$ is the derivative of the effect compartment concentration over time and k_{e0} is both the drug transfer rate constant and the elimination rate constant. This compartment relates to the effect site concentration of the drug. Lastly, effect site concentration is related to the drug effect in the brain with a non-linear Hill Sigmoid function,

$$E(t) = E_0 + (E_{max} - E_0)\frac{C_e(t)^\gamma}{C_e(t)^\gamma + C_{e,50}(t)^\gamma}, \quad 1 \leq \gamma. \tag{1.3}$$

where E_0 represents the value when drugs are absent, i.e. BIS index 100, E_{max} represents the largest possible drug concentration, yielding BIS index 0, $C_{e,50}$ is the effect site drug concentration that gives the effect $E(t) = 50$, and γ is the Hill parameter [Soltesz et al., 2020]. The total amount of parameters in this model, combining (1.1), (1.2) and (1.3), are the following:

$$\boldsymbol{\theta} = (k_{10}, k_{12}, k_{21}, k_{13}, k_{31}, V_1, k_{e0}, C_{e50}, \gamma)^T \tag{1.4}$$

Reduced parameter PKPD model structure

Another proposed model structure [Silva et al., 2010], describing the joint effect of propofol and remifentanil in the human body, is presented in this section. The model has fewer parameters than the traditional PKPD model.

Pharmacokinetics For modelling the pharmacokinetics, a linear third order continuous model is used, see (1.5).

$$C_e(s) = \frac{k_1 k_2 k_3 \alpha^3}{(s + k_1\alpha)(s + k_2\alpha)(s + k_3\alpha)} U(s) \tag{1.5}$$

where $U(s)$ is the Laplace transform of the input signal, i.e. propofol or remifentanil, k_1, k_2 and k_3 are predefined and determine the ratio between the poles, and α is the pole location selected to be a parameter.

Pharmacodynamics In order to describe the Depth of Anaesthesia, (1.5) C_e^p for propofol is combined into a nonlinear function as follows

$$E = E_0 + (E_{\max} - E_0)\frac{1}{1 + (mv^p(t))^\gamma} \tag{1.6}$$

where

$$v^p = \frac{C_e^p}{C_{e,50}^p}, \tag{1.7}$$

and $C_{e,50}^p$ is a fixed value. The total amount of parameters in this model, combining (1.5) and (1.6) are hence

$$\theta = (\alpha_p, m, \gamma)^T \tag{1.8}$$

1.4 Estimation theory

Bayesian Inference

In order to obtain estimations of parameters for this work, Bayesian inference methods were used. In Bayesian inference, the goal is to fit a model with parameters $\boldsymbol{\theta}$ to a data-set y. The result can be summarized in a probability distribution of the model parameters, in this case, a posterior distribution.

To make a probability statement about a parameter given some data y, a joint probability distribution for $\boldsymbol{\theta}$ and y is needed. This distribution is described as (1.9).

$$p(\boldsymbol{\theta}, y) = p(\boldsymbol{\theta})p(y|\boldsymbol{\theta}) \tag{1.9}$$

where $p(\boldsymbol{\theta})$ is the prior distribution and $p(y|\boldsymbol{\theta})$ is the sampling distribution. The prior distribution describes a distribution of beliefs before having access to any data. The sampling distribution, also referred to as the likelihood, describes the probability that data y is observed given that the proposed model with parameters $\boldsymbol{\theta}$ is true.

Conditioning the parameters on the observed data y, using (1.9), yields Bayes' rule, describing the posterior distribution

$$p(\boldsymbol{\theta}|y) = \frac{p(\boldsymbol{\theta}, y)}{p(y)} = \frac{p(\boldsymbol{\theta})p(y|\boldsymbol{\theta})}{p(y)} \tag{1.10}$$

where $p(y)$ is the sum over all possible values of $\boldsymbol{\theta}$. Due to this factor being independent of $\boldsymbol{\theta}$, it is usually omitted, yielding the unnormalized posterior density,

$$p(\boldsymbol{\theta}|y) \propto p(\boldsymbol{\theta})p(y|\boldsymbol{\theta}) \tag{1.11}$$

This is the fundamental formula for Bayesian inference [Gelman et al., 2013]. Typically, explicit solutions to solve for the posterior density are not available. When explicit solutions are unavailable, the distributions can be approximated with sampling methods. If enough samples exist, any important information about a distribution can be recovered. Therefore, approximation methods are widely used, one of which is the Markov Chain Monte Carlo (MCMC) sampling method [Wang and Park, 2020].

Markov Chain Monte Carlo

Monte Carlo Sampling Monte Carlo sampling is a method that models complex systems through the use of repeated random sampling. If a large number of realisations are produced, the true distribution of a process can be approximated according to the Law of Large Numbers.

Markov Chain A Markov Chain is a chain of variables in which the current value is dependent only on the previous value according to the Markov Property, (1.12).

$$P(X_t = i|X_{t-1} = j, X_{t-2}, \cdots, X_1) = P(X_k = i|X_{k-1} = j) \tag{1.12}$$

Metropolis-Hastings Algorithm Metropolis-Hastings is a Markov Chain simulation method. The algorithm in this work is based on independent proposals with acceptance-rejection rules in order for the Markov Chain to converge to the posterior distribution. This is achieved in the following steps:

1. A starting point, θ^0, is drawn from a prior distribution, $p_0(\theta)$.

2. For each iteration t;

   a) A proposal value, θ^*, is sampled from a proposal distribution $J_t(\theta^*|\theta^{t-1})$ at time t. This value is not dependent of the previous position of the Markov Chain, hence being an independent proposal.

   b) The ratio between the current position and the previous is calculated as follows

   $$r = \frac{p(\theta^*|y)J_t(\theta^*|\theta^{t-1})}{p(\theta^{t-1}|y)J_t(\theta^{t-1}|\theta^*)} \tag{1.13}$$

   c) The current value of the Markov Chain is then set according to (1.14).

   $$\theta^t = \begin{cases} \theta^*, & \text{with probability } \min(r, 1) \\ \theta^{t-1}, & \text{otherwise} \end{cases} \tag{1.14}$$

   In other words, if the current proposal value has a larger probability than the previous, the value is accepted. However, if it is not, the previous value is set as the current state in the chain [Gelman et al., 2013].

The acceptance rate of the Metropolis-Hastings algorithm can be calculated by keeping track of the number of acceptances in 2 c) and dividing them by the total number of iterations, t. The acceptance rate for the Metropolis-Hastings algorithm should lie between $10-60\%$ [McElreath, 2016].

MCMC Markov Chain Monte Carlo method is obtained by combining the Monte Carlo random sampling method with Markov Chains generated with the Metropolis-Hastings algorithm. The proposed value in step 2 a) of the Metropolis-Hastings algorithm is generated through the Monte Carlo method. Allowing the currently generated number to influence the next value is in agreement with the Markov Property, and the stationary part of the produced Markov Chain represents the posterior distribution of interest, $p(\theta|y)$.

Figure 1.2 represents an example of convergence of the Metropolis-Hastings algorithm with a trace plot (left) and the distribution plot (right) of the MCMC sampling.

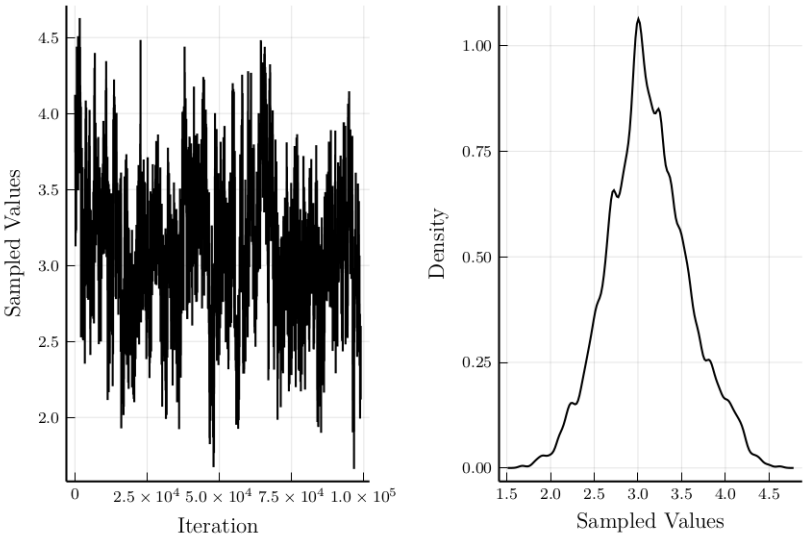

Figure 1.2 An example of the Monte Carlo random sampling method with Markov Chains generated with the Metropolis-Hastings algorithm. The left figure shows the trace plot and the right figure shows the distribution plot.

2

Methodology

This thesis focused on evaluating parameter identifiability for the PK part of the traditional PKPD model using the proposed Eleveld model. The parameters that were estimated correspond to (1.1), leaving the pharmacodynamic parameters k_{e0}, C_{e50} and γ from (1.4) out. Since the linear model is used as an input to the non-linear model, examining the linear part only as a starting point is motivated. The analysis can be parted into two main tasks;

1. Simulating data with the model, adding Gaussian noise, and then estimating the model parameters using Bayesian inference. Gaussian noise was added in order to obtain more realistic data points. Identification was performed using MCMC sampling and the estimated parameters were compared to the true values[1], which were calculated using the Eleveld model.

2. Attempting to create simulations for all 1033 subjects from the Eleveld article in the same manner as the authors did [Eleveld et al., 2018]. The method for this simulation differs from the one above by being without approximations and applicable for the entire data-set acquired by the studies from the article. Once the simulation was performed, further analysis was planned, such as estimating the PK parameters from real data using LS to be able to compare them to the values obtained by calculation of the Eleveld model.

2.1 The Eleveld Model

Eleveld et al. [Eleveld et al., 2018] developed a PKPD model using the traditional model structure to predict propofol concentrations and BIS values which can be used for a broad, diverse population. The model is based on actual data collected from 30 published studies that include a total of 1033 subjects. All studies included PK measurements and 5 of them also contained BIS measurements. The parameter values for an individual can be calculated using this model by supplying information

[1] The values which were used for the simulations, and are hence referred to as the true value.

about the subject's age, height, weight, gender and if additional drugs other than propofol were used as well as if the samples are venous or arterial.

The authors applied their proposed model for propofol prediction for all 1033 subjects by calculating the six parameters required for the PK part of the model and having logged rates and amounts for the registered times from each study as inputs to the system which in turn outputted the predictions. To do these predictions, the software NONMEM (ICON Development Solutions, Ellicott City, MD, USA) was used. The predicted propofol concentrations were plotted against the observed concentrations, and the result can be seen in Figure 2.1.

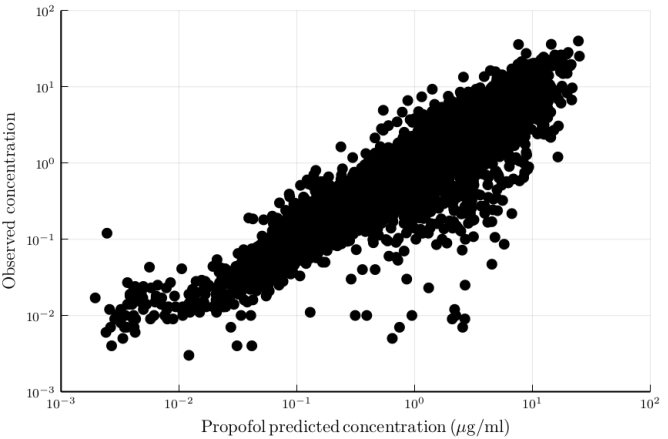

Figure 2.1 Predicted plasma concentration (obtained using NONMEM) against the observed plasma concentration for all 1033 subjects which were available in the Eleveld collection of data.

2.2 Parameter Estimation using MCMC sampling

In this section, the reader is familiarized with the approach which was used to estimate parameters from noisy simulations based on the Eleveld model.

Simulation

The simulations were coded using the programming language Julia and are based on the proposed Eleveld model for anaesthesia. They were compared with real measurements in order to confirm that the simulated data is as realistic as possible.

In order to simulate data points to be used as the target, studies, in which the propofol concentration in blood was measured, were used as a starting point. The studies described what doses were injected and at what times the plasma concentrations were extracted. To replicate these studies with the Eleveld model, the doses,

u, were used as an input into the system PK, which in turn outputted C_p, see Figure 2.2. The output C_p was generated using lsim from the package ControlSystems.jl and the system was discretized with sampling time 1 s. Thereafter, specified points according to the measurements in the respective study were extracted and used for MCMC sampling. This method was used due to two reasons:

- To check if the Eleveld model is able to reproduce the shape of the real data.
- To create a target distribution that can be generated in the same way as the observations.

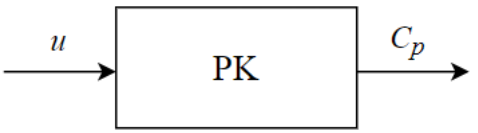

Figure 2.2 Block diagram of pharmacokinetic system, where u is the dose input and C_p is the plasma concentration of propofol.

In the first study, conducted by Struys et al. [Struys et al., 2007], seven points were measured over a time span of five minutes for each subject after injecting a bolus dose of 2.5 mg/kg during 10 seconds. The points in time were: 0, 30, 60, 120, 180, 240, and 300 s. The number of points as well as the doses are presented in Table 2.1.

In the second study, conducted by Schnider et al. [Schnider et al., 1998], 23 points were measured over a time span of 600 minutes for each subject after injecting a bolus dose of 2 mg/kg during 20 seconds followed by a continuous injection of 2 μg/kg starting at time 60 minutes and stopping at 120 minutes. The time points in which the concentration of propofol was measured were: 0, 1, 2, 4, 8, 16, 30, 60, 62, 64, 68, 76, 90, 120, 122, 124, 128, 136, 150, 180, 240, 300, and 600 min. The number of points as well as the doses are presented in Table 2.1.

Table 2.1 Table of studies used to replicate data points as targets for parameter estimations

	Number of points	Dose
Struys et al.	7	Bolus (2.5 mg/kg for 10 s)
Schnider et al.	23	Bolus + Injection (2 mg/kg for 20 s + 2 μg/kg for 60 min)

The subject information of the data obtained by Struys and Schnider are visualized in Table 2.2. Using this subject information, the PK parameter values calculated with the Eleveld model are presented in Table 2.3 for the Struys study, and 2.4 for Schnider.

Table 2.2 Subject information from each study used to obtain calculated parameter values using the Eleveld model. Propofol was the only drug injected and the samples are arterial.

	Struys	Schnider
Gender (F/M)	F	F
Age (yr)	48	34
Weight (kg)	58	46.3
BMI	22.7	18.7

Table 2.3 True parameter values obtained using the Struys subject in the Eleveld model calculations.

Parameters	True value
k_{10} (1/s)	0.004402
k_{12} (1/s)	0.007568
k_{21} (1/s)	0.002907
k_{13} (1/s)	0.002582
k_{31} (1/s)	8.988e-05
V_1 (ml)	5885

Table 2.4 True parameter values obtained using the Schnider subject in the Eleveld model calculations.

Parameters	True value
k_{10} (1/s)	0.004063
k_{12} (1/s)	0.007393
k_{21} (1/s)	0.002299
k_{13} (1/s)	0.002324
k_{31} (1/s)	7.557e-05
V_1 (ml)	5386

Parameter estimation

To identify the model described in (1.1), parameter estimation was performed using MCMC with the Metropolis-Hastings algorithm. The parameters to be estimated were

$$\boldsymbol{\theta} = (k_{10}, k_{12}, k_{21}, k_{13}, k_{31}, V_1)^T. \tag{2.1}$$

For each of the studies, multiple cases with different prior distributions for the parameters and noise levels on the generated propofol plasma concentration data were used in order to estimate the PK parameters. The two most relevant cases are described more in detail below. The parameter estimation was coded by using the package Gen.jl.

Case I The plasma concentration data noise was selected to be 0.1 μg propofol, and narrow prior distributions for the MCMC sampling were selected. In this case, narrow implies that the distribution is roughly in the same order as the true parameter values. This case was included in the thesis in order to explore whether the parameters would be identified if the prior distributions are narrow. The distributions from Case I are given in Table 2.5.

Case II The plasma concentration data noise was selected to be 0.1 μg propofol, and wide prior distributions for the MCMC sampling were selected. In this case, wide implies that the distribution for most parameters, except for the volume, is about a thousand times lager than the true parameter values.This case was included in the thesis in order to explore whether the parameters would be identified if the prior distributions are wide. The distributions from Case II are given in Table 2.5. The prior for the parameter V_1 was not changed between Case I and II due to the value being less than 10000 regardless of the prior interval.

Table 2.5 Prior distributions for each of the parameters that are to be estimated in all cases.

Parameter	Prior Case I	Prior Case II
k_{10}	$U(0, 0.01)$	$U(0, 4)$
k_{12}	$U(k_{13}, 0.01)$	$U(k_{13}, 8)$
k_{21}	$U(k_{31}, 0.01)$	$U(k_{31}, 3)$
k_{13}	$U(0, 0.01)$	$U(0, 3)$
k_{31}	$U(0, 0.001)$	$U(0, 0.1)$
V_1	$U(0, 10000)$	$U(0, 10000)$

Presentation of Results

Three chains with length 10000 for the narrow prior case 30000 and for the wide prior case were created. The latter chain was chosen to be longer in order to allow for convergence since the span of possible values for the parameters is larger. Every case was repeated three times, yielding 3 x 2 posterior distributions for one parameter in total. The results of the cases for each of the parameters were presented by:

1. Calculating the acceptance rates for the Metropolis-Hastings algorithm to find out if it is in accordance to the desired theoretical value.

2. Removing 10 % of the first iterations of the Markov Chain in order to get its stable state and plotting every 10th sample of the remaining chain.

3. Plotting the approximated posterior distribution.

4. Extracting the last value of the chain and creating data points in the same way that the simulation data was obtained. Thereafter, plotting the points in the same graph as the true simulation values, which were obtained by the Eleveld PK model.

5. Plotting the Bode diagrams of each chain with the true Bode plot from the Eleveld PK model in order to be able to compare the dynamics of the system with estimated parameters with the true system dynamic.

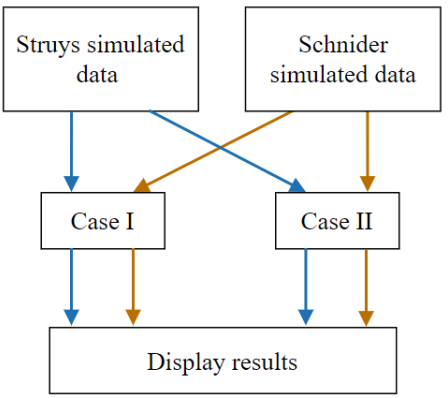

Figure 2.3 A visualisation of the method used in order to estimate parameters using MCMC sampling.

Figure 2.3 shows a visualization of the method used in order to estimate the parameters using MCMC described in this section.

2.3 Replicating Eleveld simulations

In this section, the reader is familiarized with the approach that was used to attempt to replicate Figure 2.1. The reason why replicating this plot was used as a starting point was to be able to reliably proceed with Least Square optimization as an alternative to the method applied by the software which was used in the Eleveld article to estimate parameters.

Interpretation of Data

All data used by Eleveld et al. is available for download. It contains various information about each subject from the time at which they received anaesthetic drugs to when the anaesthesia reached emergence. In order to calculate the true PK parameters for each subject, the following information collected from the data-set was used; age, height, weight, gender, if additional drugs other than propofol were used and if the samples are venous or arterial. To obtain inputs to the system, the time, amount and rate columns available in the data were important. Each row represents an event in time where either the concentration was measured, an amount was injected, a rate was changed or all of the mentioned events occurred. An example of the first row in the data-set is presented in Table 2.6

Table 2.6 An example of the first row in the data-set with information about all 1033 subjects. CP is the propofol concentration in the plasma, M1F2 is if the subject is male (1) or female (2) and TECH is whether there was an additional drug injected (2) or not (1).

Time (min)	CP (μg/ml)	Amount (mg)	Rate (mg/min)	Age (yrs)	Weight (kg)	Height (cm)	M1F2	TECH
0	0	39.398	236.34	59	64	166	2	2
0.167	0	8.862	52.98	59	64	166	2	2
0.333	0	3.921	23.52	59	64	166	2	2
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮

Discretization of Continuous Time Systems

The simulations are based on an exact solution from discretization of state-space differential equations. This method was used because it is possible to calculate the time in which a specific rate or amount was given to a patient and the sampling rate between consecutive time measurements. A continuous system

$$\begin{aligned} \dot{q}(t) &= A_c q(t) + B_c u(t) \\ y(t) &= C_c q(t) + D_c u(t) \end{aligned} \tag{2.2}$$

with solution

$$q(t) = e^{A_c t} q(0) + \int_0^t e^{A_c (t-\tau)} B_c u(\tau) d\tau \tag{2.3}$$

has the discrete time equivalent

$$\begin{aligned} q[n+1] &= A_d q[n] + B_d u[n] \\ y[n] &= C_d q[n] + D_d u[n] \end{aligned} \tag{2.4}$$

where A_d and B_d are obtained through

$$A_d = e^{A_c T_s} \text{ and } B_d = \left(\int_0^{T_s} e^{A_c \tau} d\tau \right) B_c \tag{2.5}$$

with sampling period T_s [Wittenmark et al., 2002], that in this case corresponds to the time between two measuring points. These calculations were performed for the

entire data-set in Julia, using the package ControlSystems.jl and obtaining matrices A_d, B_d through the method c2d(Gc, Ts) for each time iteration in the data.

Once the predictions for the propofol concentrations were obtained, the results were plotted in the same manner as Figure 2.1, i.e. predicted concentration against observed concentration in a figure with logarithmized x- and y-axis.

All code that was produced for the thesis is available on GitLab [Gojak, 2021].

3

Results

The results are presented in two sections for each of the main tasks in the thesis; parameter estimation using MCMC sampling for both test cases described in Chapter 2, and replicating simulations for future LS parameter estimation.

3.1 Parameter Estimation using MCMC sampling

Since the parameter estimation using MCMC sampling was applied to simulated data based on two studies, the results are presented for each study used as a starting point below.

Struys

The acceptance rates for each parameter in every chain created for the Struys data estimation is presented in Table 3.1.

Case I This case represents MCMC sampling with narrow prior distributions, as seen in Table 2.1, with a propofol concentration of 0.1 μg. Three chains were created, whose trace plots can be viewed in Figure 2.5. Their corresponding distribution plots are found in Figure 3.2. By choosing the last parameter value in the chain from the trace plots for each chain, three new simulations were created and are plotted in Figure 3.3 and the Bode plot for each system can be seen in Figure 3.4. Each chain is plotted with the same colour throughout all figures in order for all results to be easily compared. The acceptance rates for the parameters from the Metropolis-Hastings algorithm are presented in Table 3.1.

The results for Case I using data simulated with the Struys subject show that parameters k_{21}, k_{12} and V_1 are converging to the values that were used when creating the simulations. The other parameters in this case have chains that neither converge towards the true value, nor towards similar values among themselves. Although their Bode plots differ in phases between each chain, the simulations created with the estimated parameters fit the observed data very well, as seen in Figure 3.3.

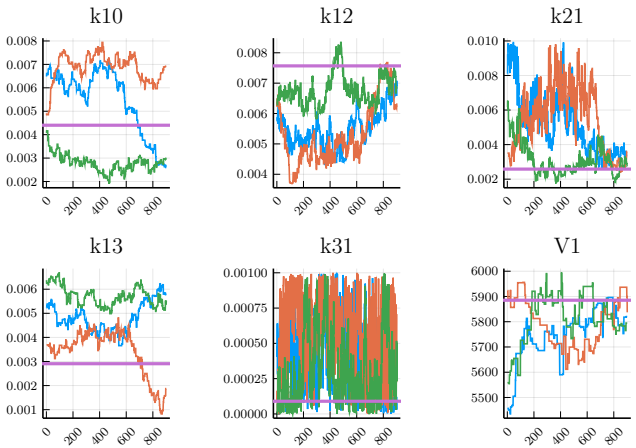

Figure 3.1 The trace plots of three chains for each parameter in Case I. Every set of chains is represented by the same colour. The horizontal purple lines are the true parameter values according to the Eleveld model calculations. In each subplot, the x-axis represents every tenth iteration sample after 10% of the chains were removed, and the y-axis represents the sampled values.

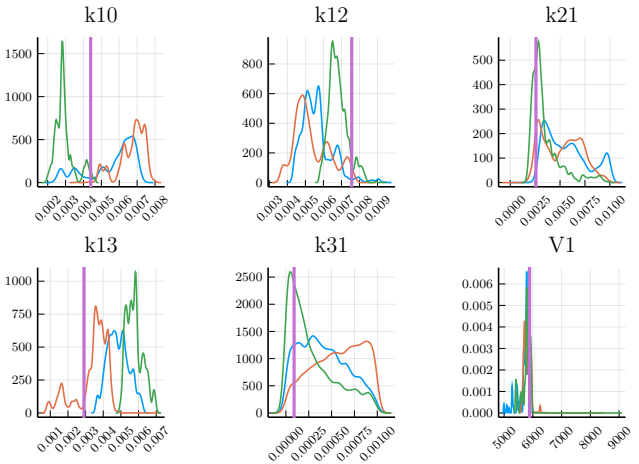

Figure 3.2 The distribution plot of three chains for each parameter in Case I. Every set of chains is represented by the same colour. The vertical purple lines are the true parameter values according to the Eleveld model calculations. In each subplot, the x-axis represents the sampled values, and the y-axis represents the density.

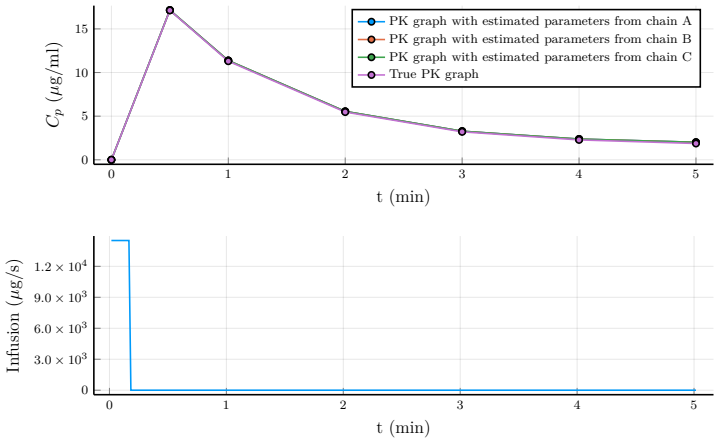

Figure 3.3 The true PK graph plotted with the PK graphs created with the estimated parameters from each chain in Case I. The lower plot shows the input to the system.

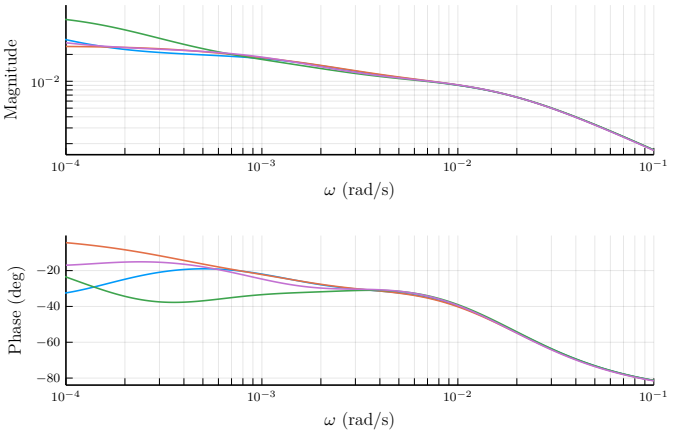

Figure 3.4 The true Bode plot (purple) with the Bode plots created with the estimated parameters from each chain in Case I.

Case II This case represents MCMC sampling with wide prior distributions, as seen in Table 2.1, with a propofol concentration of 0.1 μg. The trace plots for each chain can be seen in Figure 3.5 and the distribution plots in Figure 3.6. Figure 3.7 represents the simulations created using the last value from each chain in the PK-model and the Bode plots for each system can be seen in Figure 3.8. Each chain

is plotted with the same colour throughout all Figures in order for all results to be easily compared. The acceptance rates for the parameters from the Metropolis-Hastings algorithm are presented in Table 3.1.

For this case, the values between each chain for all parameters differ more than in Case I. In Case II, the only parameter whose chains converge towards similar values is k_{31}, and the value is off by a factor close to 20 from the true value. All other parameters are both poorly estimated and converge towards different values. The Bode plots show that the three estimated systems and the true system differ both in terms of magnitude and in terms of phase. Even though the estimated parameters are very different from the parameters used to simulate the data, they fit the data very well, as seen in Figure 3.7.

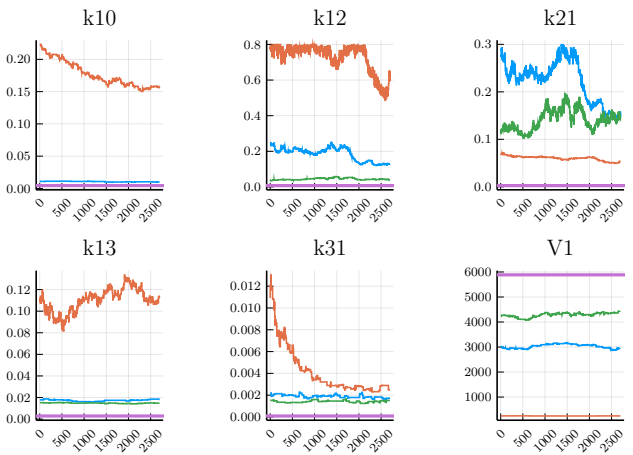

Figure 3.5 The trace plots of three chains for each parameter in Case II. Every set of chains is represented by the same colour. The horizontal purple lines are the true parameter values according to the Eleveld model calculations. In each subplot, the x-axis represents every tenth iteration sample after 10% of the chains were removed, and the y-axis represents the sampled values.

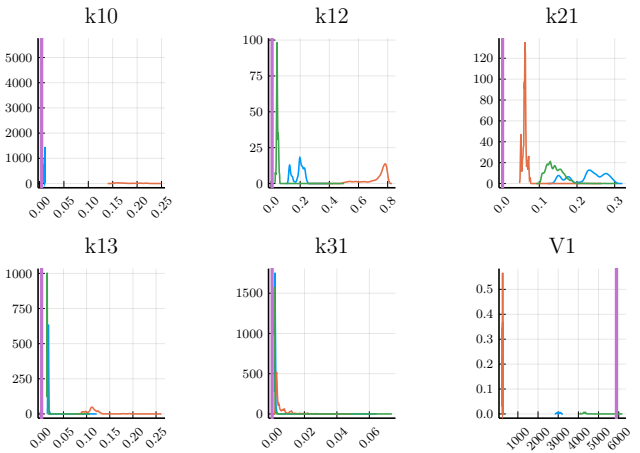

Figure 3.6 The distribution plot of three chains for each parameter in Case II. Every set of chains is represented by the same colour. The vertical purple lines are the true parameter values according to the Eleveld model calculations. In each subplot, the x-axis represents the sampled values, and the y-axis represents the density.

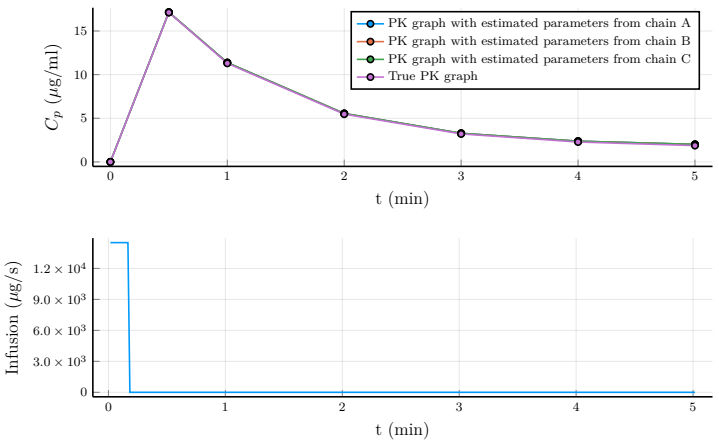

Figure 3.7 The true PK graph plotted with the PK graphs created with the estimated parameters from each chain in Case II. The lower plot shows the input to the system.

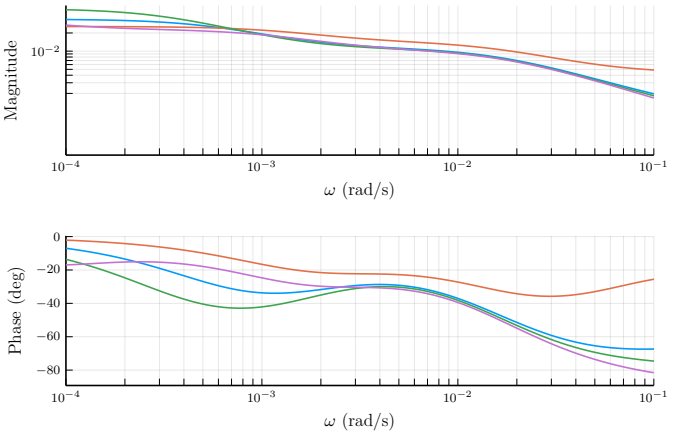

Figure 3.8 The true Bode plot (purple) with the Bode plots created with the estimated parameters from each chain in Case II.

Schnider

The acceptance rates for each parameter in every chain created for the Schnider data estimation is presented in Table 3.2.

Case I This case represents MCMC sampling with narrow prior distributions, as seen in Table 2.1, with a propofol concentration of 0.1 μg. Three chains were created, whose trace plots can be viewed in Figure 2.5. Their corresponding distribution plots are found in Figure 3.10. By choosing the last parameter value in the chain from the trace plots for each chain, three new simulations were created and are plotted in Figure 3.11 and the Bode plot for each system can be seen in Figure 3.12. Each chain is plotted with the same colour throughout all Figures in order for all results to be easily compared. The acceptance rates for the parameters from the Metropolis-Hastings algorithm are presented in Table 3.2.

For this case, parameters k_{21}, k_{13} and V_1 show convergence towards the true parameter values for most chains. The other parameters lie close in what value they are estimating between each chain, however, their convergence is not close in regards to the true values. The systems created with the different set of chains are resulting in similar Bode diagrams, see Figure 3.12, and the fit to the observed data using the estimated parameters is very good, see Figure 3.11.

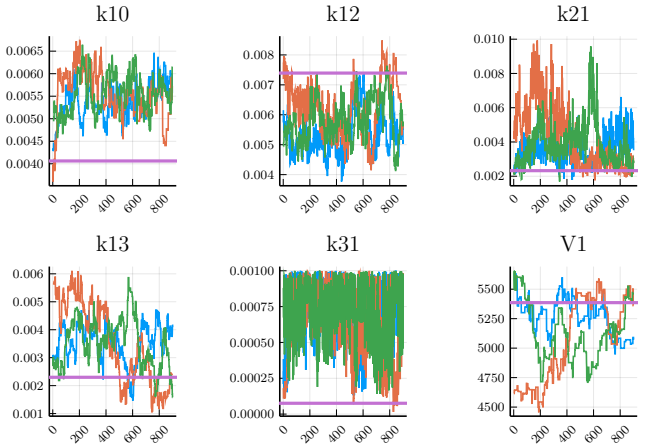

Figure 3.9 The trace plots of three chains for each parameter in Case I. Every set of chains is represented by the same colour. The horizontal purple lines are the true parameter values according to the Eleveld model calculations. In each subplot, the x-axis represents every tenth iteration sample after 10% of the chains were removed, and the y-axis represents the sampled values.

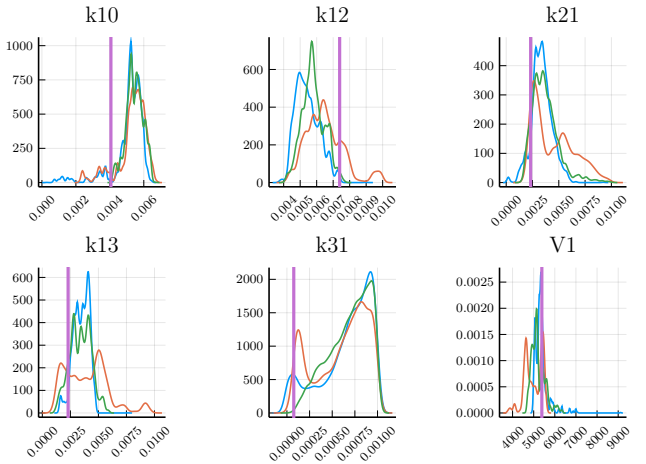

Figure 3.10 The distribution plot of three chains for each parameter in Case I. Every set of chains is represented by the same colour. The vertical purple lines are the true parameter values according to the Eleveld model calculations. In each subplot, the x-axis represents the sampled values, and the y-axis represents the density.

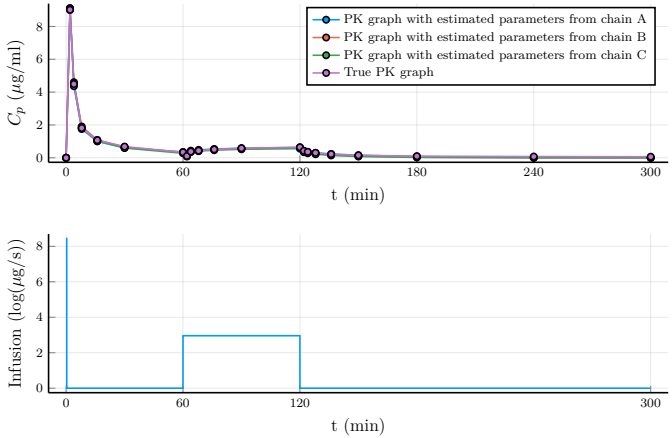

Figure 3.11 The true PK graph plotted with the PK graphs created with the estimated parameters from each chain in Case I.

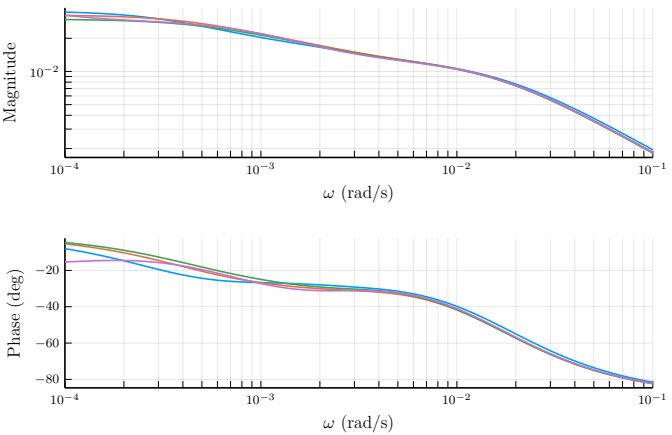

Figure 3.12 The true Bode plot (purple) with the Bode plots created with the estimated parameters from each chain in Case I. The lower plot shows a logarithmized input to the system in for visualization reasons.

Case II This case represents MCMC sampling with wide prior distributions, as seen in Table 2.1, with a propofol concentration of 0.1 μg. The trace plots for each chain can be seen in Figure 3.13 and the distribution plots in Figure 3.14. Figure 3.15 represents the simulations created using the last value from each chain in the PK-model and the Bode plots for each system can be seen in Figure 3.16. Each

chain is plotted with the same colour throughout all Figures in order for all results to be easily compared. The acceptance rates for the parameters from the Metropolis-Hastings algorithm are presented in Table 3.2.

The results in Case II for Schnider show that all parameters are converging towards similar values, however none of the estimated values are close to the true values that were calculated when creating the simulated data that was used as observed data. The system dynamics are similar for all three trials in magnitude, and differ slightly in phase as seen in Figure 3.16. The plotted PK graphs that were created using estimated parameters from each chain in Case II are fitting the observed data very well.

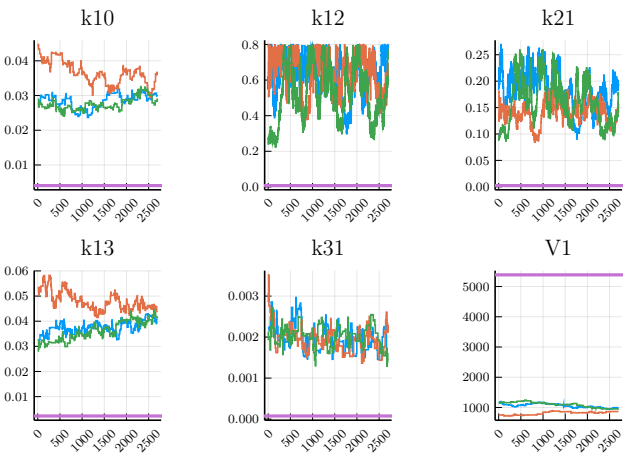

Figure 3.13 The trace plots of three chains for each parameter in Case II. Every set of chains is represented by the same colour. The horizontal purple lines are the true parameter values according to the Eleveld model calculations. In each subplot, the x-axis represents every tenth iteration sample after 10% of the chains were removed, and the y-axis represents the sampled values.

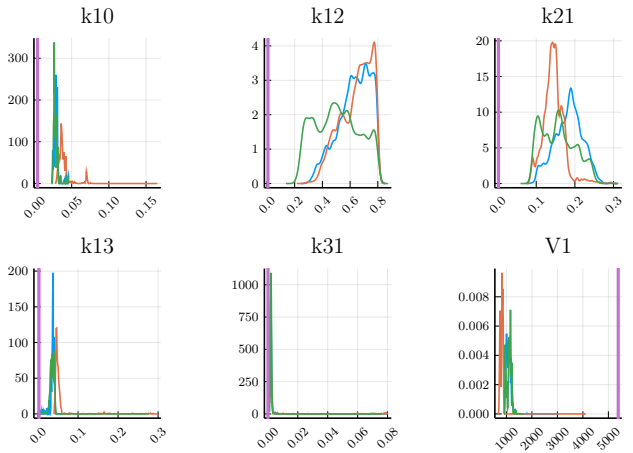

Figure 3.14 The distribution plot of three chains for each parameter in Case II. Every set of chains is represented by the same colour. The vertical purple lines are the true parameter values according to the Eleveld model calculations. In each subplot, the x-axis represents the sampled values, and the y-axis represents the density.

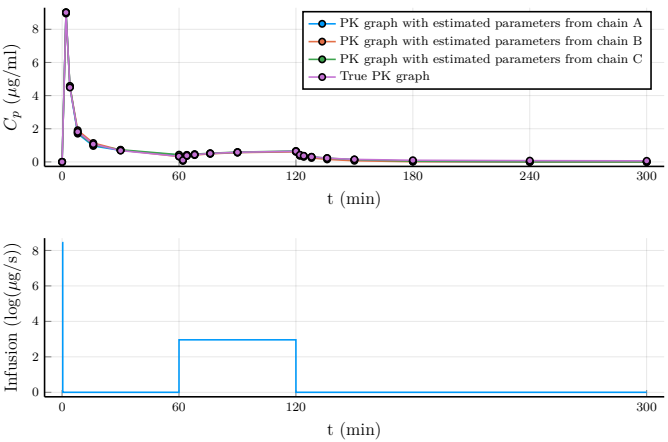

Figure 3.15 The true PK graph plotted with the PK graphs created with the estimated parameters from each chain in Case II. The lower plot shows a logarithmized input to the system in for visualization reasons.

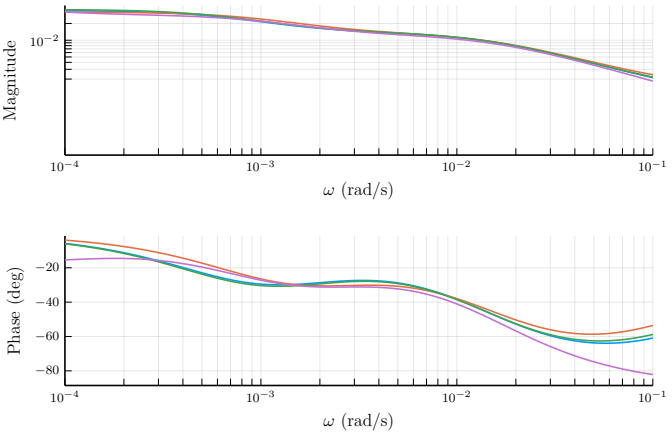

Figure 3.16 The true Bode plot(purple) with the Bode plots created with the estimated parameters from each chain in Case II.

Table 3.1 Acceptance rates for all parameters for both Case I and II in the Struys simulated data.

	Case I			Case II		
	A (%)	B (%)	C (%)	A (%)	B (%)	C (%)
k_{10} (1/s)	2.65	2.65	2.89	0.09	1.0	0.063
k_{12} (1/s)	8.14	6.43	8.23	1.47	6.29	0.51
k_{21} (1/s)	10.07	10.28	5.65	3.83	0.71	4.11
k_{13} (1/s)	2.81	3.01	2.69	0.24	2.03	0.17
k_{31} (1/s)	32.59	43.49	24.11	0.35	0.77	0.25
V_1 (ml)	0.84	0.90	0.77	0.48	0.033	0.67

Table 3.2 Acceptance rates for all parameters for both Case I and II in the Schnider simulated data.

	Case I			Case II		
	A (%)	B (%)	C (%)	A (%)	B (%)	C (%)
k_{10} (1/s)	4.22	3.8	4.26	0.42	0.64	0.53
k_{12} (1/s)	9.13	13.37	9.31	9.81	10.8	8.37
k_{21} (1/s)	11.55	13.06	12.39	6.53	5.6	5.38
k_{13} (1/s)	4.59	4.77	4.91	0.89	1.56	0.82
k_{31} (1/s)	36.2	37.41	42.51	0.81	1.16	0.76
V_1 (ml)	1.64	1.52	1.65	0.43	0.26	0.32

3.2 Replicating Simulations for LS parameter estimation

The result of replication of Figure 2.1 is visualized in Figure 3.17 and shows the actual Eleveld predictions and the replicated Eleveld prediction that was obtained through this thesis in one plot. The results show that although the simulated Eleveld predictions are similar to the predictions from the NONMEM software, they are not identical or close to identical.

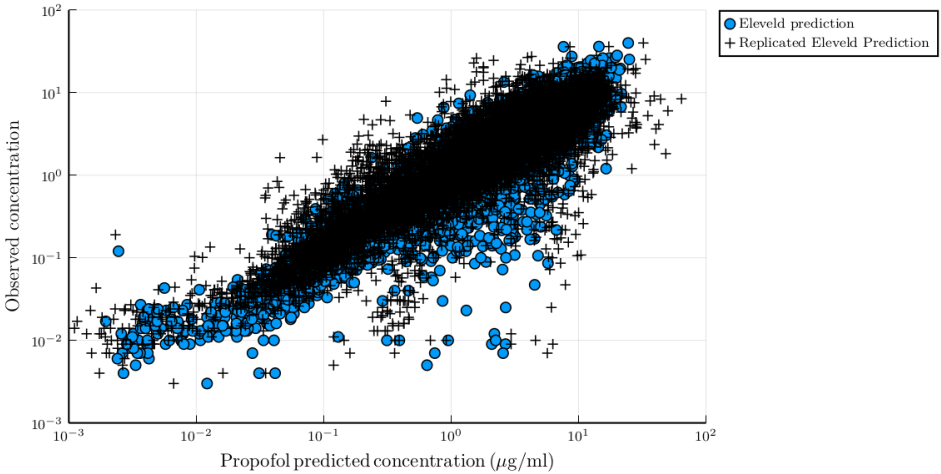

Figure 3.17 Replicated Figure 2 from the Eleveld article. The blue dots show the predictions obtained in the article using NONMEM, whereas the black crosses show what was obtained in this thesis based on exact solutions from discretization of the state-space differential equations implemented in Julia.

4

Discussion

This thesis aimed to provide further insight on parameter identifiability of a recently proposed model by Eleveld et al. for closed-loop control systems in anaesthesia. The model is based on the standard PKPD structure, with PK being a LTI system and PD being described by a non-linear Hill function. Only the linear part of the model was investigated in this work. Pharmacokinetic modelling in this case aims to predict the propofol concentration in the blood plasma for a subject that undergoes anaesthesia. Since there are six parameters in this structure, see (2.1), it is desirable to analyze the identifiability in order to comment on the usefulness of applying this model for closed-loop control systems in anaesthesia. Therefore, data was simulated using the proposed Eleveld model with additional Gaussian noise and the parameters were identified using MCMC sampling. Once the planned work focusing on individual models was finished, preparatory work was started for analysing identifiability of the population model proposed by Eleveld. A framework for simulating this model was set up in Julia, and this framework will allow for identifying parameters using other methods than the one used in the original article. This direction constitutes early work in progress, with nominal results presented above.

Identifiability with simulated data

For the identification of parameters using simulated data with noise, two studies with different amounts of points and different duration were used. The performance of identification is interesting in a case with both short duration and few points (i.e. Struys), as well as in cases with longer duration and more points (i.e. Schnider). Identifying a model with as few points as seven, using six parameters, is expected to suffer from overparameterization. Therefore, the behaviour of convergence for the different chains in Figure 3.5 are not surprising. Using more points would make identification better and this is partially confirmed in Figures 3.9 and 3.13 from the Schnider simulations. During the ongoing work, it was concluded that the priors chosen for the Metropolis-Hastings algorithm using MCMC sampling was important. Ideally, given that the chain can reach convergence, the width of the prior distributions used for initialization should not matter. Since this was not the case, two prior distributions were chosen to be presented as results in this work. No matter

the priors and the different values obtained from each chain, all simulations with the estimated parameters could fit the simulated data very well, as seen in Figures 3.3, 3.7, 3.11 and 3.15. This suggests that there are many parameter values that can fit the data and that the calculated Eleveld model parameters are not uniquely describing the system. Further supporting this conclusion are the acceptance rates from the Metropolis-Hastings algorithm. They are, for most parameters in most chains and cases, very low, implying that the MCMC sampling process does not reach a reliably estimated value.

Replicating Eleveld simulations

Considering that the simulated data was created using a model which is said to describe real data, identification of real data would be even worse due to reasons such as disturbances other than added noise. To look into identification of real data, the aim was to make use of the data which was available from the Eleveld article that contained PK measurements and information from 1033 subjects in total. The results of attempting to replicate the propofol predicted concentration seen in Figure 2.1 show that the predictions made in this thesis are not identical as the results in the article. Differences between the predictions in the article and from this work lie mainly in the software that was used to simulate data. Eleveld et al. used a software frequently which is common for parameter estimation of models within anaesthesia, NONMEM, whereas the replication in this thesis was performed using Julia. In addition to this difference, Eleveld et al. combined sequential infusion records if they were separated by < 1 s and infusion rates differed by 0.5 mg/min in order to speed up execution. This was not done in the replication, however, it should not be the main reason for the two to vary to that extent and it is hence more likely that the differences are a product of the implementations in the softwares. The scope of the thesis only allowed for insufficient simulations when replicating Figure 2 in the Eleveld article, and further analysis would be required to fully understand how the NONMEM predictions are obtained, by looking into the NONMEM code documentation.

4.1 Future work

The result of this thesis suggest that a model structure with six parameters is not practically identifiable from representative data. Therefore, suggestions on future work would be to look into if model structures with less parameters, such as the model reduced parameter PKPD model structure described in Chapter 1.

Other interesting future extensions would be to investigate how allowing for other population pharmacokinetic model structures than the one in Eleveld (chosen more or less ad hoc) would affect model fit. If the replication of Figure 2.1 would be improved, it would be interesting to use these simulations in order to look at the Hessians and the LS at the optimum which would give information about how

identifiable the system is. Another suggestion would be to use LS optimization to estimate parameters based on the data-set that was provided in the Eleveld article in order to compare the obtained parameters to the calculated parameters obtained from the Eleveld model.

5

Conclusion

This work aimed to evaluate parameter identifiability for the pharmacokinetic part of the PKPD model that is commonly used to describe the time course of drug effects on the body during anaesthesia. The results show that a model structure using six parameters for pharmacokinetics is not practically identifiable from representative data.

Identifiability was examined from simulated data using several patients with varying excitation between patients and where some data-sets had many measurements whereas others had few. The method therefore represents a range that is on different spectrums of challenging in regards to parameter identifiability.

Despite the mentioned levels of challenge to identify the model, no trial was able to find the parameter values used in simulations for the full set of parameters. The identified values were. nevertheless, fitting the observed data very well, and it was therefore concluded that a model structure with six parameters is overparameterized.

A model that causes this much uncertainty when it comes to identifiability suggests that perhaps the traditional PKPD model structure should not be used for closed-loop control systems in anaesthesia. An alternative, and suggestion for future work, would be to instead look into model structures that require less parameters.

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Identifiability of pharmacological models from data

Abstract

In order to automate anaesthesia in patients using propofol, closed-loop control systems with models that describe the time course of the drug effects on the body are required, usually being represented by pharmacokinetics and pharmacodynamics (PKPD). This thesis focused on evaluating parameter identifiability for the PK part of the model, using a model proposed by Eleveld et al. that has six parameters. Different sets of data were simulated with said model and Gaussian noise was added. To identify the parameters in the simulated data, Markov Chain Monte Carlo with the Metropolis-Hastings algorithm was applied for a set of different test cases. The results show that the estimations are dependent on the choice of priors and that the system is not uniquely identifiable. Although the estimated values differed from the parameters which were used for simulating data, the estimated parameters were able to fit the observed data very well in all trials. The conclusion of this work is that a PKPD model structure using six parameters is not practically identifiable and suggestions for future work would be to investigate whether a structure with fewer parameters could be more suitable for closed-loop control systems in anaesthesia.

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